USACEHR FINAL REPORT

TEST TITLE: EPA / IAG DW97938354-01-0
PBPK modeling in medaka with bromodichloromethane (BDCM) and the six month flow-through exposure of BDCM to medaka

DATA REQUIREMENT: Tests were conducted according to USACEHR Standing Operating Procedures, IACUC approved Animal Use Protocols, and USACEHR Scientific Protocols

AUTHORS: Ms. Margaret W. Toussaint
Dr. Jason Boyd
Dr. Jeff Fisher

REPORT DATE: December 20, 2001

LABORATORY IDENTIFICATION: U. S. Army Center for Environmental Health Research (USACEHR)
568 Doughten Drive
Fort Detrick, MD 21702-5010

INTERNAL PROJECT NUMBERS: Tests 108-001 and 108-002

STUDY SPONSOR: U.S. EPA
Office of Water
Washington, DC

20020114 009

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	20 December 2001	Final Report, 20 December 2001

4. TITLE AND SUBTITLE
EPA / IAG DW97938354-01-0 PBPK modeling in medaka with bromodichloromethane (BDCM) and the six month flow-through exposure of BDCM to medaka

5. FUNDING NUMBERS
EPA / IAG DW97938354-01-0

6. AUTHOR(S)

Margaret W. Toussaint, Jason Boyd, and Jeff Fisher

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

US Army Center for Environmental Health Research
568 Doughten Drive
Fort Detrick, MD 21702-5010

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Environmental Protection Agency
Office of Water
Health and Ecological Criteria Division
1200 Pennsylvania Avenue NW, MC 4304
Washington, DC 20460

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*
Bromodichloromethane (BDCM) was tested at 0, 1.5, and 15 mg/L in the medaka (*Oryzias latipes*) model in a static exposure (<9 hours) and a flow-through exposure (six months). At the conclusion of the static exposure, fish tissue and blood were assayed for BDCM. A preliminary physiologically based pharmacokinetic (PBPK) model was built to describe the absorption, disposition, metabolism, and excretion of BDCM in medaka. Kinetic predictions from the PBPK model were linked with selected pharmacodynamic responses. Prior to BDCM dosing for the long-term exposure, half of the fish were initiated with diethylnitrosamine (DEN). After 72 hours BDCM exposure, a subset of fish were used for cell proliferation assessment. When treated fish were statistically compared to control fish, no significant cell proliferation was found. Near test termination, the 15 mg/L BDCM medaka exhibited abnormal behaviors. At test conclusion, all fish were examined histologically. Tissue changes in treated fish were statistically compared to those of control fish. Liver neoplasia was not a significant endpoint in any uninitiated treatment group. Statistically significant endpoints were found in 15 mg/L BDCM groups, regardless of DEN treatment, and included changes in the gallbladder, liver, bone, gill, kidney, and ovary.

14. SUBJECT TERMS
bromodichloromethane, BDCM, medaka, fish, *Oryzias latipes*, PBPK, alternative animal model, drinking water disinfection byproduct, diethylnitrosamine, cell proliferation

15. NUMBER OF PAGES
60

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

GOOD LABORATORY PRACTICE STATEMENT:

These tests were not conducted to meet the requirements of 40 CFR 160 (EPA-FIFRA) or 40 CFR 792 (EPA-TSCA). To the best of my knowledge, these tests were conducted in accordance with USACEHR Standing Operating Procedures, IACUC approved Animal Use Protocol, and USACEHR Science Protocol.

Paul L. Knechtges 12/20/01

Dr. Paul L. Knechtges Date
Director of Science and Technology

QUALITY ASSURANCE STATEMENT:

There is not an active quality assurance unit at USACEHR, however all data from USACEHR tests were recorded in USACEHR notebooks and are available for review.

Paul L. Knechtges 12/20/01

Dr. Paul L. Knechtges Date
Director of Science and Technology

REPORT APPROVAL:

The work presented in this report fulfills the final reporting requirement for EPA / IAG DW97938354-01-0.

Paul L. Knechtges 12/20/01

Dr. Paul L. Knechtges Date
Director of Science and Technology

TABLE OF CONTENTS

SUMMARY

Bromodichloromethane (BDCM) was tested in the medaka fish (*Oryzias latipes*) model in a short-term and a long-term exposure. The short-term exposure lasted <9 hours with the fish tissue and blood assayed for BDCM at the conclusion of the exposure and this data was used to build a physiologically based pharmacokinetic model (PBPK) for BDCM uptake in medaka. The long-term exposure lasted six months and included a 48-hour initiation/promotion stage with diethylnitrosamine (DEN). At the conclusion of the long-term exposure, the fish tissues were assessed histopathologically for determination of chemical dosing effects.

The short-term exposure (USACEHR Test 108-001) used the following BDCM test concentrations: 0, 1.5, and 15 mg/L. Twenty same gender fish were dosed in each 1.5 L of test solution. There were three replicates of each concentration and gender. Six-month old fish were used for this experiment. Fish length and weights were determined at animal necropsy, as well as weights for blood, liver, spleen, kidney, gill, and muscle. Samples were sealed in glass headspace vials and then analyzed for BDCM content. Summarized BDCM tissue data was provided to statistical modelers and a PBPK model was developed. This model describes the absorption, disposition, metabolism, and excretion of BDCM in medaka. Kinetic predictions from the PBPK model were linked with selected pharmacodynamic responses.

The long-term exposure (USACEHR Test 108-002) tested the following BDCM concentrations: 0, 1.5, and 15 mg/L. Juvenile fish were dosed with either 0 or 10 mg/L of DEN for 48 hours, given 24 h to recover in processed well water, then moved to the BDCM dosing tanks. Fish assignment was determined by DEN initiation and by BDCM level, with three replicates of each combination. The initial number of fish in each flow-through aquarium was 30. After 72 hours of BDCM dosing, 5 fish were removed from each replicate for labeling with 5′-bromodeoxyuridine (BrdU) to assess cell proliferation. The selected fish underwent a 72-hour exposure to 75 mg/L BrdU, followed by euthanasia, sectioning, staining, and counting of the proliferating liver cells. Results were analyzed statistically. No BDCM treatment effects were found for cell proliferation. The remaining 25 fish per replicate were continuously dosed with BDCM for six months. Each entire fish was preserved and

assessed histopathologically for tissue changes between control and BDCM-dosed groups. Findings were analyzed statistically. Briefly, statistically significant findings were found in the 15 mg/L BDCM groups, regardless of DEN concentration. These significant findings included changes in the gallbladder, liver, bone, gill, kidney, and ovary. Liver neoplasia was not a significant endpoint in any uninitiated treatment group.

In conclusion, BDCM tissue levels were established for short-term exposed fish for 0, 1.5, and 15 mg/L BDCM. A preliminary PBPK model for BDCM in the medaka was developed. It represents the first PBPK model for a small fish that distinguishes between different tissue groups. Data to support either compartmental or PBPK models for small fish are based on 'lumped' kinetic data, which is usually the entire fish. The experimental design of this project allowed development and partial validation of a true PBPK model for the medaka. This modeling effort provided insights into important species extrapolation issues related to exposure and dosimetry of BDCM.

While long-term fish exposure to two concentration levels of BDCM alone did not cause neoplasia, significant findings were seen at the cellular level in the gallbladder, liver, bone, gill, kidney, and ovary in fish dosed with 15 mg/L BDCM. Publication of this work in the open literature is pending.

BACKGROUND

Previous work by the US Army Center for Environmental Health Research (USACEHR) with Japanese medaka (*Oryzias latipes*) exposed to 0, 0.015, 0.15, and 1.5 mg/L bromodichloromethane (BDCM) in aquarium water for nine months showed that intrahepatic concentrations of BDCM were roughly equivalent to the concentration of BDCM in aquarium water (Toussaint et al., 2001c). USACEHR proposed a two-phase study to determine uptake (Phase I) and depuration (Phase II) kinetics with medaka and BDCM. This IAG covered the Phase I portion of the project. USACEHR planned to conduct the fish exposures and perform sample analyses, while an extramural collaborator at Wright Patterson Air Force Base built the physiologically based pharmacokinetic (PBPK) model for medaka.

PROJECT DESCRIPTION

PBPK model development: Mature Japanese medaka were statically exposed to BDCM <9 hours at three BDCM concentrations. The proposed number of fish per treatment level was 20 males and 20 females (40 fish per treatment x 4 treatments = 160 fish. The proposed BDCM treatment levels were 0, 1.5, 15, and 150 mg/L. Blood and tissue (gill, liver, muscle, spleen, and kidney) samples removed from these fish were to be chemically analyzed for BDCM and corrected for sample volume. All raw data were summarized in spreadsheets for statistical modeling.

Six month bioassay: Juvenile Japanese medaka were exposed to two concentrations (1.5 and 15 mg/L) of BDCM in a continuous flow-through dosing system. Prior to BDCM dosing, half of the sample groups were statically exposed to 10 mg/L diethylnitrosamine (DEN) for 48 hours. This level of DEN has been shown to alter cells (initiation) but does not promote neoplasia (Hinton et al., 1988). After 28 days of BDCM dosing, 5 fish were removed from each tank for assessment of cell proliferation. The remaining 25 fish per replicate continued with BDCM dosing throughout the six-month test duration. At test termination, the fish were grossly observed and then prepared for histopathology. The pathology results were analyzed statistically to compare treated fish to control fish at the tissue level.

INTRODUCTION

BDCM is a trihalomethane that is frequently found drinking water as a disinfection by-product. At the time

the project was proposed, BDCM was reported as a mammalian liver and kidney carcinogen when high concentrations (25 to 50 mg/kg)were administered via gavage to rodents(NTP, 1987). These BDCM concentrations are several orders of magnitude higher than actual drinking water levels of 0.067 mg/L reported by Borum et al (1998). A need existed to perform animal studies at BDCM concentrations closer to drinking water levels (Boorman et al., 1999).

Alternative animal models such as fish are a natural choice for testing aqueous solutions. Fish have been shown to be sensitive to trace levels of contaminants in aquatic media (Gardner et al., 1990; Metcalfe 1989; Twerdok et al., 1997; Toussaint et al., 2001b). As water-dwelling organisms, fish are immersed in the exposure solution, with dosing occurring through dermal, oral, and, most significantly, through respiratory routes.

Japanese medaka (*Oryzias latipes*) are hardy, small in size, easy to culture, and have a relatively short time-to-tumor response. Medaka are reproductively mature at three months of age, and an exposure duration of six months encompasses the majority of the active growth and development phase of the fish life cycle. Sections of the entire animal will fit on two to three microscope slides so that examination of each tissue is possible in its anatomical context. The low rate of spontaneous neoplasms in medaka ($\leq$0.3%) aids in the interpretation of bioassay results (Hawkins et al., 1995).

Research began on this project in August 1999. The animal exposure portion of the experiment at USACEHR ended in May 2000, while statistical modeling was completed December 2001. Submission of this work for publication is planned for 2002.

MATERIALS AND METHODS

Animal Care. Research was conducted in compliance with the Animal Welfare Act, and other Federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, National Academy Press, Washington, DC, 1996, in facilities that are fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International.

Japanese medaka were supplied from USACEHR in-house cultures and were reared according to USACEHR Standing Operating Procedures, as described previously (Toussaint

2001a). Fish culture conditions were: water temperature 25±1°C, water flow of 100 mL/min of an aerated, hard, processed groundwater, an 18/6 hr light/dark cycle with full spectrum fluorescent lighting, and an age-related amount of fish flake food and live brine shrimp fed daily.

Test Materials. BDCM (CAS No. 75-27-4) of 99.8% purity was obtained from Aldrich Chemical Company, Milwaukee, WI. Under test conditions, BDCM did not break down to form other compounds, as demonstrated by chemical analyses of aquaria water. The analysis of BDCM for aqueous and tissue samples was performed using a flame ionization detector interfaced to a model 6890 capillary gas chromatograph (both from Hewlett-Packard, Wilmington, DE) equipped with a model 7694 automatic static headspace sampler and fused silica capillary column (30 m x 0.25 mm inner diameter) coated with cross-linked 1% methylsilicone gum phase, film thickness, 0.33 um (Hewlett-Packard). All stocks and standard solutions were prepared fresh daily. Sample analysis has been previously described (Toussaint et al., 2001a). Triplicate 5 mL aliquots of the 40 mL aqueous samples were analyzed. The detection limit for this gas chromatography method was 0.001 mg/L and the average percent recovery was 95%.

DEN (CAS No. 55-18-5) of >99% purity was obtained from Sigma Chemical Company, St. Louis, MO. The analysis of DEN was performed using gas chromatography on a Hewlett Packard (HP) 5880A gas chromatograph with a flame-ionization detector and an HP 19392A integrator. The detection limits were <1 mg/L and the percent recovery was 105%.

BrdU (CAS No. 59-14-3) of >99% purity was obtained from Sigma Chemical Company, St. Louis, MO. The analysis of BrdU was performed by high performance chromatography (HPLC) on an HP 1050 series HPLC equipped with variable wavelength detector, autosampler, and HP 3396A integrator. The detection limit was 1.77 mg/L and the percent recovery was 99.3%.

Test 108-001: Fish Blood and Tissue Analyses. After 4 to 9 hours of BDCM exposure, fish were euthanized and tissues harvested. Fish blood was collected, liver, gill, muscle, kidney, and spleen were excised from each animal, weighed, sealed in 10 mL glass headspace vials, and then stored at 0°C until analysis. Due to their small size, spleens and kidneys were pooled by organ type within each replicate. Approximately 1500 tissue samples were chemically analyzed for BDCM. Thawed samples were individually denatured in 5 mL of 2% (w/v) sodium dodecyl

sulfate at 60°C for 2 hr. Headspace analysis by capillary gas chromatography immediately followed as described above. The detection limit for this gas chromatography method was 0.001 mg/L and the percent recovery was 95%.

Test 108-001: Test Design. For Test 108-001, the age of the mature fish used for this one-day experiment was six months of age. The fish were not fed during the exposure. Prior to the test, the population of fish was separated into same gender groups. Randomization of 20 males to each of 9 test vessels and of 20 females to each of another 9 test vessels was done using USACEHR's computerized "RANDOM" program. A summary of the experimental design for Test 108-001 is shown in Table I. The planned duration for this experiment was 4 hours.

Table I. Test 108-001 Test Design

Group ID	Gender	BDCM Treatment Level
1	male	15 mg/L
2	male	15 mg/L
3	male	15 mg/L
4	female	15 mg/L
5	female	15 mg/L
6	female	15 mg/L
7	male	1.5 mg/L
8	male	1.5 mg/L
9	male	1.5 mg/L
10	female	1.5 mg/L
11	female	1.5 mg/L
12	female	1.5 mg/L
13	male	0 mg/L
14	male	0 mg/L
15	male	0 mg/L
16	female	0 mg/L
17	female	0 mg/L
18	female	0 mg/L

Test 108-001. PBPK Modeling Methods. Concentrations of BDCM were modeled in various tissues, including blood, liver, muscle, and gill. Remaining tissue was lumped together and represented as 'other' compartment. Metabolic parameters, Vmax and Km, for metabolism in the liver were taken from the rat (Lilly et al., 1998); Vmax was scaled from the reference value in the rat using the relationship of reference value raised to the 0.75 power and multiplied by body weight of the fish. Cardiac output was taken from a reference value in a one kilogram rainbow trout (Nichols et al., 1996) raised to the 0.75 power and multiplied by body

weight. Blood flow through tissues was determined by multiplying the relative volume of the organ by the body weight scaled cardiac output; thus, blood flow through the various tissues was also scaled. Adjustments to the model were made in order to provide better fits of model-generated concentrations of BDCM in tissues as compared to assayed or measured BDCM concentrations in tissues.

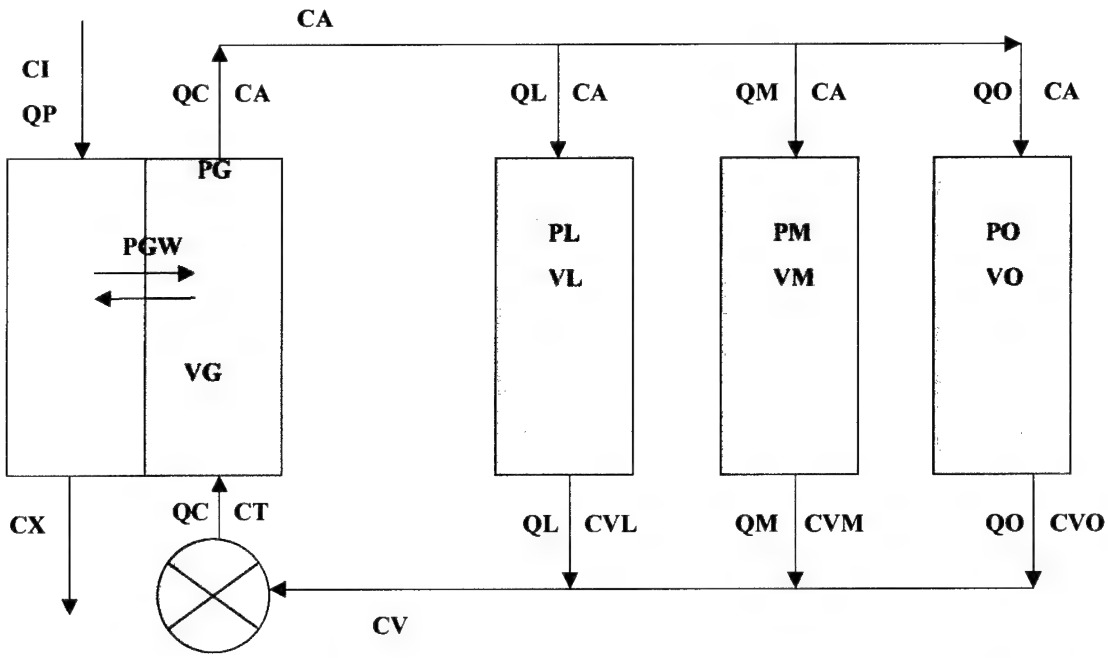
Partition coefficients were estimated by calculating the concentration ratio of tissue/blood for the muscle, gill, and liver in the low dose group (1.5 mg/L BDCM). The water/blood ratio was determined using measured water concentrations. The 'other' compartment represents a lipophilic compartment. BDCM has modest lipophilicity in rat fat tissue (Lilly et al., 1998). In the medaka, no fat tissue was removed for analysis. Our modeling efforts suggest that a fat depot probably exists for BDCM in the medaka. We were unable to simulate the kinetic behavior of BDCM in the medaka fish without this assumption. Six months of effort was devoted to developing experimental methods to measure partition coefficients of BDCM in small pieces of medaka tissue with little success.

The differential equations that constituted the structural model to simulate the pharmacokinetics of BDCM are shown in Figures I and II. A full list of all the parameters used in the model may be found in Table II. A good fit was defined as model predicted BDCM tissue concentrations falling within one standard deviation of the measured tissue concentration. The model simulation needed to be robust and to fit all tissue concentration profiles for both the 1.5 and 15 mg/L BDCM treatment groups.

Figure I: Differential equations used to model the concentration of bromodichloromethane in the Japanese medaka (*Oryzias latipes*)

```
dAG/dt = QC(CT - CA) + QP*GEE(CI*PGW - *CG/PGW)
dAM/dt = QM(CA - AM/(VM*PM))
dAL/dt = QL(CA - (AL/(VL*PL)) - RAMX)
RAMX = dAMX = VMAX*(AL/(VL*PL))/(KM + (AL/(VL*PL))
dAO/dt = QO(CA - (AO/VO*PO))
CA = AG/VG*PB
CV = (QM*(AM/VM*PM) + QL*(AL/VL*PL) + QO*(AO/VO*PO))/QC
```

Figure II: Structural model of the physiologically based pharmacokinetic model for bromodichloromethane in the Japanese medaka (*Oryzias latipes*)



Model terms end with the first letter of the tissue with which they are associated (G, L, M, O, A, and V for gill, liver, muscle, other, arterial, and venous). Model terms beginning with Q are flow rates (L/h) such that QC is cardiac output, QL is blood flow to the liver, etc. QP is rate of intake into the gill. Model terms beginning with C represent concentrations (mg/L); arterial concentrations enter tissues and leave as venous concentrations (eg CA enters liver and exits as venous liver concentration, CVL). CI and CX are inspired and expired concentrations; CT is a transit term used in ACSL code and is equivalent to CV. Partition coefficients begin with P, end with the first letter of the tissue with which they are associated.

Test 108-002: Test Design. For Test 108-002, the initial age of the medaka was 16 days ± 1 day, and the fish were fed throughout the study. Food was withheld 24 h prior to the six-month histopathology sacrifice.

Randomization of thirty juvenile fish to each of the 18 test vessels was done using USACEHR's computerized "RANDOM" program. A summary of the experimental design for Test 108-002 is shown in Table III. Under the continuous flow-through dosing regimen, sufficient BDCM remained in solution during testing to maintain dosage levels. Due to the large number of test aquaria needed for the test design, two solenoid-controlled proportional diluters were used to deliver test material. Stock solutions of 1785 and 1036 mg/L BDCM were made daily by adding neat BDCM to processed well water. The BDCM stocks were stirred for 24 ± 2 h in sealed glass containers, then pumped into a diluter dosing

bottle. Approximately 25 L of BDCM stock were needed for each test day.

Table II: Model parameters and description for the physiologically based pharmacokinetic-pharmacodynamic model of bromodichloromethane in the Japanese medaka (*Oryzias latipes*)

Scalable rates		
QCC	Cardiac output	2.07
QPC	Rate of uptake at gill	7.06
Fractional blood flows (%CO)		
QLC [b]	Fractional blood flow to liver	0.03
QMC [b]	Fractional blood flow to muscle	0.6
QGC	Fractional blood flow to gill	1
Relative volumes (%BW)		
VGC	volume of gill	0.1
VLC [b]	volume of liver	0.02
VMC [b]	volume of muscle	0.78
Partition Coefficients		
PGW	Gill/water	2.45
PB	Gill/blood	0.46
PL	Liver/blood	1.25
PM	Muscle to blood	0.12
PO [b]	"other" / blood	18
Metabolism		
VMAXC (mg/L/h)	Scaleable Vmax	0.0128
KM [a] (mg/L)	Michelis-Menten constant for metabolism	0.5

a taken (and adjusted) from Lilly et al., 1998
b Nichols et al., 1996

Six test aquaria were randomly assigned to each nominal concentration: 0, 1.5, and 15 mg/L BDCM. The test began when sixteen-day-old fry ($\pm$1 day) were randomized to each test aquarium, with 30 fry per five-gallon aquarium. The diluter was set to deliver 300 $\pm$15 mL to each aquarium every 3 min $\pm$15 seconds, yielding 9-10 tank volume turnovers per day.

The test began with a 48-hour exposure to 0 or 10 mg/L DEN. The fish were rinsed for 24 hours in processed well water before beginning the six-month BDCM exposure. After 28 days of BDCM exposure, 5 fish per aquarium per timepoint were removed for hepatocellular proliferation assays. The method for cell proliferation assessment has been described previously (Brennan et al., 2001). Briefly, the fish received a static exposure to 75 mg/L 5-bromo-2'-deoxyuridine (BrdU) for 72 hours, followed by euthanasia,

fixation in acetone, embedding, sectioning, staining, and reading of the slides. The remainder of the test fish received six months of BDCM exposure, followed by necropsy for histopathological evaluation.

Table III. Test 108-002 Test Design

Group ID	BDCM Treatment	DEN Treatment
1	0 mg/L	0 mg/L
2	0 mg/L	0 mg/L
3	0 mg/L	10 mg/L
4	0 mg/L	10 mg/L
5	1.5 mg/L	0 mg/L
6	1.5 mg/L	10 mg/L
7	15 mg/L	0 mg/L
8	15 mg/L	0 mg/L
9	15 mg/L	10 mg/L
10	15 mg/L	10 mg/L
11	0 mg/L	0 mg/L
12	0 mg/L	10 mg/L
13	1.5 mg/L	0 mg/L
14	1.5 mg/L	0 mg/L
15	1.5 mg/L	10 mg/L
16	1.5 mg/L	10 mg/L
17	15 mg/L	0 mg/L
18	15 mg/L	10 mg/L

Test 108-002: Chronic Histopathology. At six months of BDCM exposure, fish were euthanized with an overdose of tricaine methanesulfonate (MS-222). Fish necropsy procedures, fixation, sectioning, staining, and histopathology were as described previously (Toussaint et al., 1999). Briefly, fish were opened ventrally, flushed with Bouin's solution and sealed in tissue cassettes. After 48 hr immersion in Bouin's, the tissue was rinsed with two successive 24 hr treatments of 70% ethanol, and then held in 10% formalin. Five longitudinal step sections were cut from paraffin blocks, stained with hematoxylin and eosin, followed by microscopic evaluation of the tissue. The following tissues were assessed histologically: bone (vertebra), brain, chromaffin tissue, corpuscle of Stannius, esophagus, eye, gallbladder, gill, heart, hematopoietic tissue, interrenal tissue, intestine, kidney, liver, nares, ovary, pancreas, peripheral nerve, pineal organ, pituitary gland, pseudobranch, skeletal muscle, skin, spinal cord, spleen, stato-acoustic organ, swim bladder, testis, thymus, thyroid tissue, urinary bladder, and gross lesions.

Test 108-002: Statistical Analyses. Lengths, weights,

and histopathology data were analyzed statistically (Snedcor and Cochran, 1980; Hsu JC, 1996; McCullagh and Nelder 1983). Comparisons of length and weight data were done by one-way analysis of variance F tests. When comparing the combined controls versus each combined dose-level group the effect of multiple comparisons was accounted for by Dunnet's method. The effect of multiple comparisons was accounted for by Tukey's method. For each replication separately and for the three replications combined, standard linear regression methods were used. For histopathology endpoints, standard chi-square tests were used to compare the occurrence rates from two or more experimental groups. Fisher-exact tests were used when computationally feasible. The effect of multiple comparisons when combining two or more experimental groups was accounted for by the Bonferroni method. For each replication separately and for the three replications combined, logistic regression methods were used to see if the occurrence rate of each endpoint was related to dose level.

Archiving Requirements. Stained fish slides were archived and will be held for a minimum of five years. Chemistry samples were spent during analysis and were not archived. All raw data, data summaries, and test reports will be maintained by USACEHR for a minimum of 10 years after completion of the test report.

RESULTS AND DISCUSSION

Test 108-001: Water Quality. Single measurements of temperature, pH, dissolved oxygen, and conductivity were taken on each of the 18 test vessels at the conclusion of the exposure. Alkalinity and hardness were measured in one control tank. All measurements were within acceptable ranges. Neither pH nor dissolved oxygen levels were changed by BDCM concentration. Results were 25.1°C for temperature, 7.3 for pH, 7.5 mg/L for dissolved oxygen, 645 umho/cm for conductivity, 128 mg/L for alkalinity, and 196 mg/L for hardness.

Test 108-001: External BDCM Concentration. For Test 108-001 (PBPK test) the measured BDCM concentrations were averaged from the initial and final readings of six replicate containers at each treatment level with the following mean values and standard deviations obtained: below detection limits of 0.001 mg/L for controls, 1.82 $\pm$ 0.2246 mg/L, and 17.14 $\pm$ 2.3552 mg/L.

Test 108-001: BDCM in Fish Blood and Tissue. At the

time of fish necropsy, fish were removed from a test container and then held in clean well water until euthanasia. A team of researchers worked on each container, with an average working time of approximately 70 minutes per test container. Comparisons of measured values for individual fish tissues within each group of the beginning and final fish necropsied for each container did not show a consistent depuration trend, and it is assumed that this holding period had minimal impact on the study.

Additionally, the duration of the exposure had a wide variability due to the amount of time required for necropsy. The 15 mg/L fish had a duration range of 6.5 to 8.5 hours, the 1.5 mg/L fish had a duration range of 5.0 to 8.5 hours, and the controls had a duration range of 4.0 to 5.5 hours. Tissue concentrations for the 1500 samples are shown in Appendix I, with raw data and averages by group, by gender, and by treatment level. For example, female medaka weighing 562 mg $\pm$91 mg (mean and standard deviation) were found to have the following mean BDCM tissue levels at 15 mg/L BDCM external concentration: 8.77E+05 mg/L in blood, 2.15E+06 mg/L in liver, 4.17E+05 mg/L in muscle, 1.70E+06 mg/L in gill, 3.32E+06 mg/L in kidney, and 4.45E+07 mg/L in spleen. Similar order of magnitude findings occurred in males at the same BDCM treatment level.

Test 108-001: PBPK Model. The model simulated concentrations of BDCM in medaka fish tissues approached observed concentrations only after critical adjustments to the PBPK model were attempted and by using concentration ratios from high dosed male medaka as partition coefficients. The model code is given in Appendix II, while the simulation plots are shown in Appendix III. A term for gill extraction efficiency, GEE, was added to the PBPK model in the gill compartment to account for diffusional limitations after initial model runs produced highly exaggerated tissue concentrations. The value for GEE was based on a reported extraction efficiency of 7% for butanol in trout gills (McKim et al., 1995). This was one of the significant findings from our modeling efforts. Only a very small fraction of the 'inhaled' BDCM dissolved in water is actually taken up into systemic circulation. However, it is important to note that our approach to describing the gill/water exchange is taken from approaches used for inhaled gases that have a high water solubility and modest lipid solubility (Fisher et al., 2000). Other fish PBPK models for much larger fish describe the gill/water exchange by more rigorous methods (McKim et al., 1995; Erickson and McKim, 1990).

Initial iterations done with the maximum rate of metabolism set at the value reported in rats (Lilly et al., 1998), scaled to the 0.75 power and multiplied by body weight of the fish failed to simulate the observed BDCM concentration profiles measured in the medaka. Scaling the metabolic rate from rats to the medaka fish resulted in extremely rapid clearance of DBCM from systemic circulation. We then set the maximum rate of metabolism, Vmaxc, to zero and increased its value, in an iterative fashion, until suitable fits were seen. Adjustments to Vmaxc were carried out merely to provide better fits of the data. To determine the metabolic constants, Vmax and Km, for oxidation of BDCM in the medaka liver additional experimentation are required. Metabolism of BDCM is thought to be predominantly dependant on CPY2E1 in the rat (Allis et al., 2001). However, one report suggests that this isoform is not expressed in the medaka (Lipscomb et al., 1997). Other isoforms of the cytochrome p450 system as well as other enzymes may metabolize BDCM in the medaka.

Hepatocellular adenoma incidence rates in the medaka fish were chosen as a pharmacodynamic endpoint because of reported findings of BDCM induced liver neoplasms in rats (NTP, 1987; Dunnick et al., 1987). One of the important 'information gaps' in the use of medaka as an alternative model for rodents is understanding the differences in routes of exposure. The model derived dosimetry parameter, area-under-the-concentration-versus-time-curve for liver (AUCL), was selected for regression analysis with the percent incidence of hepatocellular adenoma found in the medaka study. There was very high linear correspondence of percent liver incidence with AUCL (r^2=1.0). Bioassay studies for the medaka were carried out over several weeks, while the pharmacokinetic study was a 4-hour study. The PBPK model was developed based on the 4-hour study and used to extrapolate to longer-term exposures that were used in the medaka bioassay study. All regression parameters relating percent incidence to the exposure metric of AUCL are presented in Table IV. More pharmacokinetic data is needed to describe the pharmacodynamic responses with a Hill equation or Weibull cumulative density function, which would provide more a more accurate description of the dose-toxic-effect relationship of BDCM (Gibaldi and Perrier, 1982; Newman, 1995).

Table IV: Pharmacodynamic regression parameters - percent effect as a function of AUCL

Exposure metric	*slope*	*intercept*	r^2
AUCL	1 x 10-6	1.48	1.00
Weekly AUCL	4 x 10-5	1.48	1.00
Daily AUCL	2 x 10-4	1.48	1.00

With further research, improvements in the PBPK-PD model can be accomplished in several areas. With more pharmacokinetic studies, a richer time course data set could be used to obtain optimized model parameters using Advanced Continuous Simulation Language (ACSL) optimization routine. The physiological parameters we used for the medaka were scaled down from large fish. Further research on the physiology (blood flows and breathing rates) of the medaka would improve the PBPK model robustness. Separate metabolic studies are required to quantify the metabolic capability of the medaka. Finally, research to quantify the diffusional limitations associated with gill mucous and gill diffusion would allow for more accurate estimates of chemical intake.

Test 108-002: Test Water Quality. Water quality parameters were measured in each test aquarium on the following frequency: daily (temperature), weekly (dissolved oxygen, pH, conductivity, alkalinity, and hardness), and monthly (ammonia). All parameters were found to be within acceptable ranges. Summarized mean values with standard deviations are 24.8 $\pm$ 0.4°C for temperature, 7.4 $\pm$ 3.2 mg/L for dissolved oxygen, 666 $\pm$ 108 umho/cm for conductivity, 0.001 $\pm$ 0 mg/L for un-ionized ammonia. The pH range was from 7.2 to 8.0 standard units.

Test 108-002: Cell Proliferation. Summarized raw data from both count labeling indices (CLI) and area labeling indices (ALI) are shown in Table V. Cell proliferation was not a significant finding when BDCM-treated fish were compared to control fish. For both ALI and CLI, there appeared to be a linear effect of BDCM and the slope appeared to be the same for both DEN=0 mg/L and DEN=10 mg/L and there appeared to be no effect of DEN adjusted for BDCM.

Table V. Area and Count Labeling Indexes Statistics by Tank

Tank	DEN	BDCM	N	area labeling mean	area labeling std dev	count labeling mean	count labeling std dev
1	0	0	5	0.0022	0.0032	0.0772	0.1094
2	0	0	5	0.0032	0.0034	0.0856	0.0867
3	10	0	5	0.0266	0.0247	0.5006	0.4436
4	10	0	5	0.0270	0.0315	0.5382	0.6415
5	0	1.5	5	0.0150	0.0110	0.2240	0.1367
6	10	1.5	5	0.0098	0.0086	0.2268	0.1844
7	0	15	5	0.0244	0.0388	0.4634	0.7192
8	0	15	5	0.0788	0.1183	1.2356	1.3473
9	10	15	5	0.1502	0.2193	2.0978	2.6063
10	10	15	5	0.0392	0.0528	0.3766	0.5084
11	0	0	5	0.0112	0.0116	0.2490	0.1888
12	10	0	5	0.0048	0.0054	0.1134	0.1101
13	0	1.5	5	0.0134	0.0128	0.2066	0.1655
14	0	1.5	5	0.0254	0.0241	0.5386	0.4974
15	10	1.5	5	0.0204	0.0206	0.2974	0.2671
16	10	1.5	5	0.0224	0.0257	0.4412	0.5684
17	0	15	5	0.0226	0.0318	0.5542	0.6573
18	10	15	5	0.0268	0.0220	0.7430	0.6261

Test 108-002: BDCM Chemical Analyses. Over the course of six months, weekly chemical analyses were performed on each aquarium. Mean measured concentrations (replicates combined) were obtained from averaging the 27 weekly BDCM measurements of all six test aquaria per treatment level to obtain the following mean values and standard deviations: 0.008 $\pm$ 0.017 mg/L (controls), 1.468 $\pm$ 0.379 mg/L, and 14.885 $\pm$ 3.178 mg/L.

Test 108-002: Fish Growth and Survival. A summary of the fish growth measurements is shown in Table VI. Mortality through the six-month exposure period was acceptable (<4%) in all control and treated groups. A one-way analysis of variance was used to see if each of the 3 groups of fish at each treatment level in each group had the same mean length and weight values. In general this appeared to be true except for the mean length among the DEN=0/BDCM=0 and DEN=0/BDCM=1.5 groups. For weight, within each treatment group, the 3 groups of fish were not significantly different from each other; for length, however, equality of the 3 tanks (25.2, 24.0 and 23.6) of the control group (DEN=0 BDCM=0) and the 3 tanks (26.2, 24.8 and 24.6) of the treatment group DEN=0 and BDCM=1.5 were significantly different from each other. Because the differences in length for the 3 replicate control groups and for the 3 replicates of the treatment group DEN=0/BDCM=1.5

were not substantial, the 3 replicate groups of fish were combined. For length, there appeared to be a BDCM effect for both DEN groups, however only the DEN=10 group showed a clear linear trend (length decreases as BDCM increases); there was a consistent DEN effect (DEN=10 is longer) but the statistical significance is strong for the BDCM=0 group, moderate for the BDCM=1.5 group, and nil for the BDCM=15 group. For weight, there appeared to be a linear BDCM effect only in the DEN=10 group (weight decreased while BDCM increased); there appeared to be a consistent DEN effect (DEN=10 is heavier than DEN=0), however, the statistical significance of this effect was strong in the BDCM=0 group while nil in the BDCM=1.5 and BDCM=15 groups.

Table VI. Test 108-002 Fish Growth Measurements

BDCM Treatment	DEN Treatment	Mean Length (mm)	Mean Weight (mg)
Controls	0 mg/L	24.3	280
Controls	10 mg/L	25.5	303
1.468 mg/L	0 mg/L	25.2	289
1.468 mg/L	10 mg/L	25.6	292
14.885 mg/L	0 mg/L	23.3	273
14.885 mg/L	10 mg/L	23.7	279

Test 108-002: Fish Histopathology. At six months of BDCM exposure, ANOVA indicated that the significant findings ($p = 0.05$) were present in multiple organ systems, as shown in Appendix IV. DEN initiation increased findings of hepatocellular adenoma were only observed in 15 mg/L males. Hepatocellular carcinoma was not significant for either DEN treatment or BDCM treatment, regardless of DEN treatment. The finding of liver basophilic foci was significant for 15 mg/L BDCM-exposed fish for both males and females. Reports in the literature indicate that basophilic foci in medaka are often likely to develop into hepatocellular adenomas (Bunton 1996; Hinton et al., 1988). For the present study, this was confirmed with 15 mg/L males but not for females. Liver neoplastic findings were not significant in either BDCM treatment level in uninitiated fish. These results suggest that BDCM does not act as a cancer initiator at either treatment level.

Findings of bile duct concretions, dilatation, and hyperplasia observed in a previous USACEHR medaka exposure to BDCM at 1.4 mg/L (Toussaint et al., 2001c) were confirmed in the current study, while gallbladder concretions were not

significant. Additionally, gill lamellae fusion was significant for all 1.4 mg/L BDCM-exposed medaka except males which had not been initiated with DEN. Males without DEN initiation showed significant levels of kidney tubular casts.

When BDCM treatment was increased to 15 mg/L, more statistically significant histology endpoints were seen. Gallbladder concretions were significant for both males and females, while gallbladder epithelium hyperplasia was significant for uninitiated females and for DEN-initiated males. Within the liver, bile duct concretions were significant for both males and females regardless of DEN treatment, while bile duct dilatation and bile duct hyperplasia were significant for most test groups. Bone malformations were common in 15 mg/L BDCM-treated fish, with the jaw and vertebrae significantly affected. Findings in the gill included fusion of gill lamellae, hyperplasia of gill epithelium, malformed arches, and malformed filaments. Significant levels of thyroid follicles were only seen in DEN-initiated males. Within the kidney, significant findings of tubular casts, tubular degeneration, and mineralization occurred independent of DEN treatment, but varied by gender. Lastly, ovarian findings of early vitellogenic stage and undeveloped ovaries were significant for females regardless of DEN treatment.

Concretion occurrence in gallbladder and bile ducts has previously been identified in BDCM-treated medaka (Toussaint et al., 2001c). Gallstones of unknown significance or etiology have also been identified in tilapia (*Oreochromic mossambicus*) (Ferguson, 1989). The occurrence of biliary concretions has been noted in monkeys, cattle, and pigs, with an origin of a crystallization nidus (Jones and Hunt, 1983). It was suggested that a nidus might result from an infectious agent such as *Pseudomonas aeruginosa,* which has been identified as the causative agent of concretions in sheep, or from particles of bile salts, calcium carbonate, cholesterol, or precipitated bilirubin. The significance of these endpoints and other chronic pathology findings in BDCM-treated medaka is unknown.

During the last six weeks of the chronic BDCM exposure, fish behavior in the 15 mg/L tanks became noticeably different from normal behavior. Observations of behavior by fish aquaria were noted and recorded in approximately one-week intervals. The control fish showed normal swimming and feeding behavior. They were distributed evenly throughout the water column. The 1.5 mg/L BDCM fish showed normal feeding behavior, although they seemed to have a heightened

response to stimuli. These fish fed throughout the water column. At 15 mg/L BDCM, abnormal fish behaviors were observed. All fish had rapid respiration and were hyperexcitable. When movement was observed, it was exaggerated and without regard to fish orientation, i.e., the fish would veer off on a 90° angle towards the top or bottom of the aquaria. These fish were not evenly distributed throughout the water column and were seen hovering at the top or resting on the bottom. Feeding only occurred at the water surface. Severe abdominal edema was seen in two fish. Spinal abnormalities such as scoliosis and kyphosis were observed, along with jaw abnormalities. DEN treated fish exhibited the same behaviors as untreated fish at each BDCM treatment level. Since these observations were not blinded, the data were not statistically analyzed; however they confirm that the 15 mg/L fish were most effected.

CONCLUSIONS

BDCM tissue levels were established for short-term exposed fish for 0, 1.5 and 15 mg/L. A preliminary PBPK model in medaka was developed. This PBPK modeling effort represents the first PBPK model for a small fish that distinguished between different tissue groups and provides insights into species extrapolation issues related to exposure and dosimetry of BDCM. Chronic exposure to 1.5 or 15 mg/L BDCM caused significant changes in fish tissue pathology after six months, with gallbladder, liver, bile ducts, kidney, ovary, gill, and bone having pathological effects. DEN initiation increased the occurrence of hepatocellular adenomas in males and basophilic foci in both genders at the 15 mg/L BDCM treatment level.

Acknowledgments. The authors thank H. Gardner, A. Rosencrance, L. Brennan, W. Dennis, R. Miller and R. Bishoff for technical assistance. The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Citations of commercial organizations or trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

REFERENCES

Allis JW, Brown BL, Zhao G, and Pegram RA. 2001, The effects of inhalation exposure to bromodichloromethane on specific rat cytochrome isosymes, Toxicology, 161(1-2):67-77.

Boorman GA, Dellarco V, Dunnick JK, Chapin RE, Hunter S, Heuchman F, Gardner HS, Cox M, and Sills RC (1999). Drinking water disinfection byproducts: review and approach to toxicity evaluation. Environ Health Perspect 107(1):207-217.

Borum D, Cox M, Javdan M, Ley ME, and Carpenter T (1998). Occurrence assessment for disinfectants and disinfection byproducts in public drinking water supplies. EPA 815/B-98-004. Final Report. Science Applications International Corporation, McLean, VA.

Brennan LM, Boncavage-Hennessey EM, Wolfe MJ, Toussaint MW, Dennis WE, Rosencrance AB, and Gardner HS (2001). An *in vivo* method for using 5-bromo-2'-deoxyuridine (BrdU) as a marker of chemically-induced hepatocellular proliferation in the Japanese medaka (*Oryzias latipes*). Toxicol Pathol, 29(3):387-397.

Bunton TE (1996). Experimental Chemical Carcinogenesis in Fish. Toxicol Pathol 24(5):603-618.

Dunnick JK, Eustis SL, and Lilja HS. 1987. Bromodichloromethane, a trihalomethane that produces neoplasms in rodents, Cancer Research 47:5189-5193.

Erickson RJ and McKim JM. 1990. A model for exchange of organic chemicals at fish gills: flow and diffusion limitations. Aquat Toxicol 18:175-198.

Ferguson HW (1989). Systemic Pathology of Fish. Iowa State University Press, Ames, IA.

Fisher JW, Dorman DC, Medinsky MA, Welsch F, and Conolly RB. 2000. Analysis of Respiratory Exchange of Methanol in the Lung of the Monkey using a Physiological Model, Toxicological Sciences, 53:185-193.

Gardner HS, van der Schalie WH, Wolfe MJ, and Finch RA (1990). New methods for on-site biological monitoring of effluent water quality. In: In Situ Evaluations of Biological Hazards of Environmental Pollutants (Sandhur SS, Lower WR, de Serres FJ, Shuk WA, and Tice RR ed). New York: Plenum, pp 61-69.

Gibaldi M and Perrier D. 1982. Pharmacokinetics, 2nd ed, p. 221-67. Marcel Dekker, Inc, New York, Basel.

Hawkins WE, Walker WW, and Overstreet RM (1995). Carcinogenicity tests using aquarium fish. Toxicology Methods 5:225-263.

Hinton DE, Couch JA, Teh SJ, and Courtney LA (1988). Cytological changes during progression of neoplasia in selected fish species. Aquat Toxicol 11:77-112.

Hsu JC. 1996. Multiple Comparisons: Theory and Methods. Chapman and Hall, London.

Jones TC and Hunt RD (1983). Veterinary Pathology. Lea and Febiger, Philadelphia, PA.

Lilly PD, Andersen ME, Ross TM, and Pegram RA. 1998. Physiologically based estimation of in vivo rates of bromodichloromehtane metabolism, Toxicology 124(2):141-52.

Lipscomb JC, Buttler GW, and Confer PD. 1997. Chloral hydrate formation in the Japanese medaka minnow, Annals of clinical laboratory science, 27(2):157-62.

McCullagh P and Nelder JA. 1983. Generalized Linear Models, Chapman and Hall, London.

McKim J, Schmeider P, and Veith G. 1985. Absorption dynamics of organic chemical transport across trout gills as related to octanol water partition coefficient. Toxicol Appl Pharmacol 77:1-10.

Metcalfe CD (1989). Tests for predicting carcinogenicity in fish. CRC Rev Aquat Sci 1:111-129.

National Toxicology Program (NTP) 1987. Toxicology and carcinogenesis studies of bromodichloromethane in F344/N rats and B6C3F1 mice, NIH publication 88-2537, NTP TR 321, U.S. Department of Health and Human Services, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Newman MC. 1995. Quantitative methods in aquatic ecotoxicology, p. 120-123. Lewis Publishers, Boca Raton, Ann Arbor, London, Tokyo.

Nichols JW, McKim JM, Lien GJ, Hoffman AD, Bertelsen SL, Elonen CM. 1996. A physiologically based toxicokinetic model for dermal absorption of organic chemicals by fish, Fund Appl Toxicol, 31:229-242.

Powers DA (1989). Fish as model systems. Science 246:352-358.

Snedcor GW and Cochran WC. 1980. Statistical methods, Seventh Edition. The Iowa State University Press. Ames, Iowa.

Toussaint MW, Brennan LM, Rosencrance AB, Dennis WE, Hoffmann FJ, and Gardner HS (2001b). Acute toxicity of four drinking water disinfection byproducts to juvenile Japanese medaka fish. Bull Environ Contam Toxicol, 66:252-262.

Toussaint MW, Rosencrance AB, Brennan LM, Beaman JR, Wolfe MJ, Hoffmann FJ, and Gardner HS (2001a). Chronic toxicity of chloroform to Japanese medaka fish. Environ Health Perspect, 109(1):35-40.

Toussaint MW, Rosencrance AB, Brennan LM, Dennis WE, Beaman JR, Wolfe MJ, Hoffmann FJ, and Gardner HS. 2001c. Chronic Toxicity of Bromodichloromethane to the Japanese Medaka (Oryzias latipes). Toxicologic

Pathology 29(6):1-8.

Toussaint MW, Wolfe MJ, Burton DT, Hoffmann FJ, Shedd TR, and Gardner HS (1999). Histopathology of a Japanese medaka (*Oryzias latipes*) chronically exposed to a complex environmental mixture. Toxicologic Pathology 27(6):652-663.

Twerdok LE, Burton DT, Gardner HS, Shedd TR, and Wolfe MJ (1997). The use of nontraditional assays in an integrated environmental assessment of contaminated ground water. Environ Toxicol Chem 9:1816-180.

U.S. EPA (2000). National Primary Drinking Water Regulations: Disinfectants and Disinfection Byproducts; Final Rule. 40 CFR Parts 9, 141, and 142. Available: http://www.epa.gov/OGWDW/mdbp/dbpfr.html [cited 7 January 2000].

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
1-1	668.9	5.4	0.028	2.59E-05	2.59E+01	10.0	0.227	1.14E-04	1.14E+02	88.1	0.296	1.68E-05	1.68E+01	25.6	0.938	1.83E-04	1.83E+02
1-2fem	738.9	none	0.097			53.6	0.079	7.37E-06	7.37E+00	55.5	0.174	1.57E-05	1.57E+01	11.8	0.130	5.51E-05	5.51E+01
1-3	528.5	4.2	0.012	1.43E-05	1.43E+01	16.1	0.259	8.04E-05	8.04E+01	68.9	0.107	7.76E-06	7.76E+00	22.8	0.166	3.64E-05	3.64E+01
1-4	640.3	3.3	0.009	1.36E-05	1.36E+01	23.8	0.372	7.82E-05	7.82E+01	35.9	0.035	4.87E-06	4.87E+00	29.7	0.584	9.83E-05	9.83E+01
1-5	718.1	6.3	0.021	1.67E-05	1.67E+01	19.5	2.545	6.53E-04	6.53E+02	64.5	0.093	7.21E-06	7.21E+00	28.3	0.230	4.06E-05	4.06E+01
1-6	463.1	3.7	0.013	1.76E-05	1.76E+01	10.7	0.069	3.22E-05	3.22E+01	55.7	0.049	4.40E-06	4.40E+00	39.6	0.452	5.71E-05	5.71E+01
1-7	562.8	6.5	0.012	9.23E-06	9.23E+00	6.6	0.039	2.95E-05	2.95E+01	58.6	0.048	4.10E-06	4.10E+00	11.0	0.063	2.86E-05	2.86E+01
1-8	673.2	6.4	0.013	1.02E-05	1.02E+01	15.8	0.894	2.83E-04	2.83E+02	48.1	0.041	4.26E-06	4.26E+00	34.3	0.291	4.24E-05	4.24E+01
1-9	481.8	4.8	0.011	1.15E-05	1.15E+01	12.7	0.047	1.85E-05	1.85E+01	47.1	0.029	3.08E-06	3.08E+00	41.2	0.068	8.25E-06	8.25E+00
1-10	554.8	2.7	0.037	6.85E-05	6.85E+01	8.8	0.012	6.82E-06	6.82E+00	58.3	0.174	1.49E-05	1.49E+01	38.9	0.044	5.66E-06	5.66E+00
1-11	480.9	2.4	0.009	1.88E-05	1.88E+01	7.6	0.073	4.80E-05	4.80E+01	66.4	0.166	1.25E-05	1.25E+01	25.4	0.460	9.06E-05	9.06E+01
1-12	533.4	2.0	0.009	2.25E-05	2.25E+01	20.5	0.041	1.00E-05	1.00E+01	52.9	0.056	5.29E-06	5.29E+00	20.7	0.101	2.44E-05	2.44E+01
1-13	428.4	4.4	0.009	1.02E-05	1.02E+01	11.5	0.142	6.17E-05	6.17E+01	41.9	0.037	4.42E-06	4.42E+00	16.7	0.110	3.29E-05	3.29E+01
1-14	569.9	3.2	0.010	1.56E-05	1.56E+01	14.9	0.048	1.61E-05	1.61E+01	62.7	0.051	4.07E-06	4.07E+00	22.1	0.165	3.73E-05	3.73E+01
1-15	562.2	2.6	0.010	1.92E-05	1.92E+01	8.4	0.047	2.80E-05	2.80E+01	82.5	0.083	5.03E-06	5.03E+00	13.0	0.040	1.54E-05	1.54E+01
1-16	484.3	6.0	0.010	8.33E-06	8.33E+00	3.7	0.013	1.76E-05	1.76E+01	46.2	0.041	4.44E-06	4.44E+00	30.5	0.234	3.84E-05	3.84E+01
1-17	622.2	6.2	0.016	1.29E-05	1.29E+01	12.5	0.082	3.28E-05	3.28E+01	89.3	0.102	5.71E-06	5.71E+00	39.8	0.206	2.59E-05	2.59E+01
1-18	498.5	3.8	0.009	1.18E-05	1.18E+01	16.6	0.014	4.22E-06	4.22E+00	42.3	0.016	1.89E-06	1.89E+00	40.9	0.013	1.59E-06	1.59E+00
1-19	494.5	4.8	0.011	1.15E-05	1.15E+01	7.5	0.030	2.00E-05	2.00E+01	61.7	0.054	4.38E-06	4.38E+00	22.2	0.291	6.55E-05	6.55E+01
1-20	524.6	3.4	0.009	1.32E-05	1.32E+01	9.3	0.022	1.18E-05	1.18E+01	74.5	0.065	4.36E-06	4.36E+00	18.5	0.092	2.49E-05	2.49E+01
1-extra	465.8	2.3	0.006	1.30E-05	1.30E+01	10.3	0.107	5.19E-05	5.19E+01	53.3	0.051	4.78E-06	4.78E+00	14.9	0.084	2.82E-05	2.82E+01
2-1	650.9	6.0	0.016	1.33E-05	1.33E+01	8.4	0.068	4.05E-05	4.05E+01	42.8	0.127	1.48E-05	1.48E+01	9.7	0.073	3.76E-05	3.76E+01
2-2	533.7	0.8	0.007	4.38E-05	4.38E+01	3.8	0.097	1.28E-04	1.28E+02	21.3	0.050	1.17E-05	1.17E+01	6.8	0.028	2.06E-05	2.06E+01
2-3	545.4	3.2	0.007	1.09E-05	1.09E+01	9.6	0.070	3.65E-05	3.65E+01	25.8	0.033	6.40E-06	6.40E+00	7.9	0.012	7.59E-06	7.59E+00
2-4	670.8	4.4	0.009	1.02E-05	1.02E+01	4.0	0.029	3.63E-05	3.63E+01	35.3	0.034	4.82E-06	4.82E+00	14.5	0.080	2.76E-05	2.76E+01
2-5	587.0	2.3	0.009	1.96E-05	1.96E+01	3.7	0.024	3.24E-05	3.24E+01	39.1	0.047	6.01E-06	6.01E+00	3.8	0.014	1.84E-05	1.84E+01
2-6	568.1	1.8	0.009	2.50E-05	2.50E+01	8.3	0.135	8.13E-05	8.13E+01	39.5	0.046	5.82E-06	5.82E+00	11.3	0.066	2.92E-05	2.92E+01
2-7	594.8	2.7	0.008	1.48E-05	1.48E+01	4.7	0.029	3.09E-05	3.09E+01	51.3	0.061	5.95E-06	5.95E+00	9.0	0.017	9.44E-06	9.44E+00
2-8	571.4	3.1	0.008	1.29E-05	1.29E+01	1.8	0.178	4.94E-04	4.94E+02	44.8	0.041	4.58E-06	4.58E+00	11.1	0.074	3.33E-05	3.33E+01
2-9	570.4	4.5	0.009	1.00E-05	1.00E+01	6.9	0.014	1.01E-05	1.01E+01	48.3	0.045	4.66E-06	4.66E+00	11.0	0.016	7.27E-06	7.27E+00
2-10	589.6	3.8	0.011	1.45E-05	1.45E+01	7.9	0.024	1.52E-05	1.52E+01	36.0	0.032	4.44E-06	4.44E+00	18.4	0.071	1.93E-05	1.93E+01
2-11	617.7	4.3	0.007	8.14E-06	8.14E+00	9.5	0.069	3.63E-05	3.63E+01	24.1	0.016	3.32E-06	3.32E+00	6.6	0.012	9.09E-06	9.09E+00
2-12	682.8	2.9	0.010	1.72E-05	1.72E+01	10.2	0.091	4.46E-05	4.46E+01	23.9	0.018	3.77E-06	3.77E+00	20.6	0.108	2.62E-05	2.62E+01
2-13	414.6	6.0	0.006	5.00E-06	5.00E+00	7.1	0.020	1.41E-05	1.41E+01	32.0	0.025	3.91E-06	3.91E+00	14.5	0.030	1.03E-05	1.03E+01
2-14	430.2	1.5	0.006	2.00E-05	2.00E+01	5.4	0.013	1.20E-05	1.20E+01	14.8	0.009	3.04E-06	3.04E+00	4.9	0.007	7.14E-06	7.14E+00
2-15	691.0	6.2	0.006	4.84E-06	4.84E+00	7.9	0.051	3.23E-05	3.23E+01	48.9	0.040	4.09E-06	4.09E+00	13.3	0.116	4.36E-05	4.36E+01
2-16	608.6	1.1	0.008	3.64E-05	3.64E+01	11.3	0.233	1.03E-04	1.03E+02	21.3	0.016	3.76E-06	3.76E+00	7.8	0.020	1.28E-05	1.28E+01
2-17	574.4	1.8	0.014	3.89E-05	3.89E+01	2.3	0.017	3.70E-05	3.70E+01	20.7	0.011	2.66E-06	2.66E+00	6.9	0.007	5.07E-06	5.07E+00
2-18	531.6	5.1	0.007	6.86E-06	6.86E+00	10.2	0.059	2.89E-05	2.89E+01	53.7	0.048	4.47E-06	4.47E+00	8.9	0.018	1.01E-05	1.01E+01
2-19	575.4	3.4	0.006	8.82E-06	8.82E+00	7.5	0.020	1.33E-05	1.33E+01	22.6	0.019	4.20E-06	4.20E+00	13.7	0.042	1.53E-05	1.53E+01
2-20	490.6	1.1	0.001	4.55E-06	4.55E+00	8.8	0.023	1.31E-05	1.31E+01	82.2	0.061	3.71E-06	3.71E+00	6.7	0.010	7.46E-06	7.46E+00

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
3-1	618.5	3.6	0.014	1.94E-05	1.94E+01	23.8	0.667	1.40E-04	1.40E+02	34.8	0.181	2.60E-05	2.60E+01	32.3	0.742	1.15E-04	1.15E+02
3-2	741.8	5.6	0.021	1.88E-05	1.88E+01	12.3	0.189	7.68E-05	7.68E+01	56.1	0.112	9.98E-06	9.98E+00	28.9	0.504	8.72E-05	8.72E+01
3-3	513.7	4.6	0.008	8.70E-06	8.70E+00	20.4	0.059	1.45E-05	1.45E+01	35.9	0.031	4.32E-06	4.32E+00	19.3	0.097	2.51E-05	2.51E+01
3-4	683.6	2.4	0.007	1.46E-05	1.46E+01	15.1	0.127	4.21E-05	4.21E+01	54.1	0.097	8.96E-06	8.96E+00	26.5	0.080	1.51E-05	1.51E+01
3-5	456.4	4.3	0.013	1.51E-05	1.51E+01	14.2	0.139	4.89E-05	4.89E+01	58.6	0.095	8.11E-06	8.11E+00	3.4	0.142	2.09E-04	2.09E+02
3-6	580.4	3.8	0.014	1.84E-05	1.84E+01	13.5	0.098	3.63E-05	3.63E+01	51.9	0.065	6.26E-06	6.26E+00	29.0	0.363	6.26E-05	6.26E+01
3-7	576.4	4.7	0.011	1.17E-05	1.17E+01	11.8	0.079	3.35E-05	3.35E+01	43.4	0.057	6.57E-06	6.57E+00	33.7	0.207	3.07E-05	3.07E+01
3-8	621.5	3.8	0.014	1.84E-05	1.84E+01	13.5	0.093	3.44E-05	3.44E+01	65.7	0.075	5.71E-06	5.71E+00	34.8	0.241	3.46E-05	3.46E+01
3-9	580.8	2.9	0.008	1.38E-05	1.38E+01	10.2	0.115	5.64E-05	5.64E+01	69.1	0.077	5.57E-06	5.57E+00	20.8	0.077	1.85E-05	1.85E+01
3-10	615.4	3.2	0.010	1.56E-05	1.56E+01	17.1	0.081	2.37E-05	2.37E+01	48.6	0.074	7.61E-06	7.61E+00	25.3	0.190	3.75E-05	3.75E+01
3-11	496.4	4.5	0.009	1.00E-05	1.00E+01	6.9	0.018	1.30E-05	1.30E+01	50.5	0.050	4.95E-06	4.95E+00	11.7	0.018	7.69E-06	7.69E+00
3-12	817.5	7.2	0.019	1.32E-05	1.32E+01	22.4	0.194	4.33E-05	4.33E+01	103.4	0.317	1.53E-05	1.53E+01	15.2	0.107	3.52E-05	3.52E+01
3-13	620.5	10.0	0.011	5.50E-06	5.50E+00	46.9	0.138	1.47E-05	1.47E+01	36.4	0.047	6.46E-06	6.46E+00	11.2	0.041	1.83E-05	1.83E+01
3-14	652.5	6.0	0.012	1.00E-05	1.00E+01	13.2	0.041	1.55E-05	1.55E+01	61.9	0.063	5.09E-06	5.09E+00	14.0	0.041	1.46E-05	1.46E+01
3-15	778.5	6.6	0.021	1.59E-05	1.59E+01	18.2	0.274	7.53E-05	7.53E+01	87.8	0.133	7.57E-06	7.57E+00	23.2	0.197	4.25E-05	4.25E+01
3-16	524.3	3.6	0.013	1.81E-05	1.81E+01	11.2	0.186	8.30E-05	8.30E+01	59.5	0.101	8.49E-06	8.49E+00	25.4	0.299	5.89E-05	5.89E+01
3-17	558.3	4.6	0.011	1.20E-05	1.20E+01	21.0	0.055	1.31E-05	1.31E+01	67.4	0.073	5.42E-06	5.42E+00	29.9	0.097	1.62E-05	1.62E+01
3-18	786.8	8.2	0.026	1.59E-05	1.59E+01	20.2	0.323	8.00E-05	8.00E+01	80.0	0.122	7.63E-06	7.63E+00	26.5	0.162	3.06E-05	3.06E+01
3-19	613.1	5.2	0.016	1.54E-05	1.54E+01	13.6	0.362	1.33E-04	1.33E+02	47.8	0.051	5.33E-06	5.33E+00	18.2	0.155	4.26E-05	4.26E+01
3-20	513.9	3.1	0.010	1.61E-05	1.61E+01	7.4	0.028	1.89E-05	1.89E+01	29.3	0.028	4.78E-06	4.78E+00	none	0.105		
4-1	533.8	3.5	0.011	1.57E-05	1.57E+01	8.2	0.113	6.89E-05	6.89E+01	37.0	0.170	2.30E-05	2.30E+01	11.9	0.312	1.31E-04	1.31E+02
4-2	593.7	5.1	0.010	9.80E-06	9.80E+00	13.9	0.147	5.29E-05	5.29E+01	33.4	0.081	1.21E-05	1.21E+01	6.9	0.035	2.54E-05	2.54E+01
4-3	667.8	4.0	0.013	1.63E-05	1.63E+01	3.8	0.161	2.12E-04	2.12E+02	35.2	0.095	1.35E-05	1.35E+01	7.9	0.045	2.85E-05	2.85E+01
4-4	693.0	2.4	0.008	1.67E-05	1.67E+01	21.6	0.120	2.78E-05	2.78E+01	44.2	0.102	1.15E-05	1.15E+01	30.4	0.278	4.57E-05	4.57E+01
4-5	612.7	4.7	0.008	8.51E-06	8.51E+00	11.3	0.180	7.96E-05	7.96E+01	51.1	0.137	1.34E-05	1.34E+01	9.2	0.125	6.79E-05	6.79E+01
4-6	811.2	3.2	0.007	1.09E-05	1.09E+01	9.0	0.146	8.11E-05	8.11E+01	51.2	0.108	1.05E-05	1.05E+01	4.9	0.037	3.78E-05	3.78E+01
4-7	513.8	2.5	0.007	1.40E-05	1.40E+01	4.5	0.028	3.11E-05	3.11E+01	48.5	0.104	1.07E-05	1.07E+01	6.9	0.026	1.88E-05	1.88E+01
4-8	473.4	2.2	0.009	2.05E-05	2.05E+01	13.7	0.061	2.23E-05	2.23E+01	31.6	0.046	7.28E-06	7.28E+00	8.3	0.071	4.28E-05	4.28E+01
4-9	599.0	1.8	0.008	2.22E-05	2.22E+01	5.3	0.013	1.23E-05	1.23E+01	47.4	0.095	1.00E-05	1.00E+01	8.7	0.067	3.85E-05	3.85E+01
4-10	442.8	4.4	0.013	1.48E-05	1.48E+01	10.8	0.040	1.85E-05	1.85E+01	19.5	0.027	6.92E-06	6.92E+00	10.1	0.025	1.24E-05	1.24E+01
4-11	521.3	7.7	0.009	5.84E-06	5.84E+00	11.4	0.069	3.03E-05	3.03E+01	28.3	0.037	6.54E-06	6.54E+00	12.4	0.065	2.62E-05	2.62E+01
4-12	672.5	1.5	0.009	3.00E-05	3.00E+01	11.5	0.080	3.48E-05	3.48E+01	36.6	0.049	6.69E-06	6.69E+00	8.0	0.026	1.63E-05	1.63E+01
4-13	694.1	4.2	0.013	1.55E-05	1.55E+01	9.7	0.027	1.39E-05	1.39E+01	22.1	0.029	6.56E-06	6.56E+00	9.2	0.014	7.61E-06	7.61E+00
4-14	619.7	4.9	0.015	1.53E-05	1.53E+01	12.8	0.077	3.01E-05	3.01E+01	36.8	0.040	5.43E-06	5.43E+00	9.7	0.034	1.75E-05	1.75E+01
4-15	559.9	1.0	0.008	4.00E-05	4.00E+01	6.6	0.015	1.14E-05	1.14E+01	30.9	0.036	5.83E-06	5.83E+00	9.2	0.025	1.36E-05	1.36E+01
4-16	488.0	1.0	0.009	4.50E-05	4.50E+01	3.9	0.014	1.79E-05	1.79E+01	27.5	0.045	8.18E-06	8.18E+00	22.4	0.134	2.99E-05	2.99E+01
4-17	459.9	1.2	0.008	3.33E-05	3.33E+01	6.1	0.013	1.07E-05	1.07E+01	57.4	0.044	3.83E-06	3.83E+00	5.8	0.016	1.38E-05	1.38E+01
4-18	667.9	0.9	0.008	4.44E-05	4.44E+01	17.3	0.110	3.18E-05	3.18E+01	49.6	0.072	7.26E-06	7.26E+00	8.5	0.017	1.00E-05	1.00E+01
4-19	461.9	2.1	0.010	2.38E-05	2.38E+01	10.7	0.040	1.87E-05	1.87E+01	34.1	0.042	6.16E-06	6.16E+00	9.1	0.024	1.32E-05	1.32E+01
4-20	491.5	1.5	0.008	2.67E-05	2.67E+01	8.7	0.038	2.18E-05	2.18E+01	54.4	0.076	6.99E-06	6.99E+00	6.4	0.020	1.56E-05	1.56E+01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
5-1	596.1	4.3	0.028	3.26E-05	3.26E+01	21.0	1.301	3.10E-04	3.10E+02	49.0	0.258	2.63E-05	2.63E+01	21.6	0.786	1.82E-04	1.82E+02
5-2	610.9	8.0	0.037	2.31E-05	2.31E+01	12.3	0.200	8.13E-05	8.13E+01	34.8	0.073	1.05E-05	1.05E+01	27.6	0.386	6.99E-05	6.99E+01
5-3	530.2	4.7	0.017	1.81E-05	1.81E+01	10.6	0.198	9.34E-05	9.34E+01	33.3	0.093	1.40E-05	1.40E+01	29.4	0.718	1.22E-04	1.22E+02
5-4	706.6	6.4	0.032	2.50E-05	2.50E+01	36.7	1.162	1.58E-04	1.58E+02	55.5	0.158	1.42E-05	1.42E+01	28.2	0.333	5.90E-05	5.90E+01
5-5	595.8	2.9	0.013	2.24E-05	2.24E+01	16.7	0.221	6.62E-05	6.62E+01	58.3	0.170	1.46E-05	1.46E+01	33.4	0.898	1.34E-04	1.34E+02
5-6	652.4	2.8	0.014	2.50E-05	2.50E+01	14.4	0.277	9.62E-05	9.62E+01	63.2	0.106	8.39E-06	8.39E+00	45.3	0.627	6.92E-05	6.92E+01
5-7	509.8	7.2	0.011	7.64E-06	7.64E+00	17.0	0.047	1.38E-05	1.38E+01	48.0	0.065	6.77E-06	6.77E+00	32.6	0.169	2.59E-05	2.59E+01
5-8	545.6	3.5	0.017	2.43E-05	2.43E+01	11.2	0.095	4.24E-05	4.24E+01	47.1	0.081	8.60E-06	8.60E+00	29.7	0.278	4.68E-05	4.68E+01
5-9	450.2	4.5	0.013	1.44E-05	1.44E+01	11.3	0.010	4.42E-06	4.42E+00	37.4	0.060	8.02E-06	8.02E+00	26.8	0.337	6.29E-05	6.29E+01
5-10	499.1	1.9	0.014	3.68E-05	3.68E+01	10.2	0.033	1.62E-05	1.62E+01	62.1	0.107	8.62E-06	8.62E+00	19.4	0.115	2.96E-05	2.96E+01
5-11	366.6	3.0	0.020	3.33E-05	3.33E+01	11.2	0.223	9.96E-05	9.96E+01	36.6	0.205	2.80E-05	2.80E+01	33.2	1.058	1.59E-04	1.59E+02
5-12	647.0	5.5	0.035	3.18E-05	3.18E+01	9.5	0.072	3.79E-05	3.79E+01	40.1	0.088	1.10E-05	1.10E+01	50.4	0.212	2.10E-05	2.10E+01
5-13	439.9	3.3	0.019	2.88E-05	2.88E+01	13.5	0.232	8.59E-05	8.59E+01	52.5	0.163	1.55E-05	1.55E+01	34.0	0.478	7.03E-05	7.03E+01
5-14	498.9	5.0	0.021	2.10E-05	2.10E+01	9.5	0.132	6.95E-05	6.95E+01	54.1	0.374	3.46E-05	3.46E+01	30.0	0.131	2.18E-05	2.18E+01
5-15	451.6	2.2	0.010	2.27E-05	2.27E+01	15.3	0.040	1.31E-05	1.31E+01	52.0	0.081	7.79E-06	7.79E+00	14.8	0.030	1.01E-05	1.01E+01
5-16	462.3	4.6	0.018	1.96E-05	1.96E+01	17.9	0.112	3.13E-05	3.13E+01	46.0	0.086	9.35E-06	9.35E+00	32.7	0.157	2.40E-05	2.40E+01
5-17	435.0	2.6	0.009	1.73E-05	1.73E+01	8.1	0.089	5.49E-05	5.49E+01	63.0	0.118	9.37E-06	9.37E+00	13.3	0.079	2.97E-05	2.97E+01
5-18	508.7	4.9	0.012	1.22E-05	1.22E+01	12.6	0.086	3.41E-05	3.41E+01	53.2	0.108	1.02E-05	1.02E+01	11.1	0.027	1.22E-05	1.22E+01
5-19	478.8	3.1	0.010	1.61E-05	1.61E+01	1.9	0.010	2.63E-05	2.63E+01	54.3	0.076	7.00E-06	7.00E+00	7.2	0.324	2.25E-04	2.25E+02
5-20	435.5	2.0	0.008	2.00E-05	2.00E+01	12.8	0.035	1.37E-05	1.37E+01	59.0	0.078	6.61E-06	6.61E+00	16.6	0.065	1.96E-05	1.96E+01
6-1	654.1	2.6	0.013	2.50E-05	2.50E+01	10.4	0.134	6.44E-05	6.44E+01	43.5	0.127	1.46E-05	1.46E+01	13.6	0.072	2.65E-05	2.65E+01
6-2	687.1	4.1	0.010	1.22E-05	1.22E+01	5.1	0.072	7.06E-05	7.06E+01	31.2	0.103	1.65E-05	1.65E+01	18.0	0.355	9.86E-05	9.86E+01
6-3	538.1	2.1	0.011	2.62E-05	2.62E+01	9.7	0.080	4.12E-05	4.12E+01	32.2	0.083	1.29E-05	1.29E+01	6.3	0.041	3.25E-05	3.25E+01
6-4	640.9	1.6	0.011	3.44E-05	3.44E+01	10.0	0.100	5.00E-05	5.00E+01	30.2	0.061	1.01E-05	1.01E+01	19.2	0.216	5.63E-05	5.63E+01
6-5	584.4	6.2	0.015	1.21E-05	1.21E+01	12.5	0.711	2.84E-04	2.84E+02	45.5	0.176	1.93E-05	1.93E+01	14.7	0.116	3.95E-05	3.95E+01
6-6	567.3	4.1	0.013	1.59E-05	1.59E+01	6.0	0.041	3.42E-05	3.42E+01	32.7	0.051	7.80E-06	7.80E+00	21.0	0.204	4.86E-05	4.86E+01
6-7	706.4	4.7	0.019	2.02E-05	2.02E+01	17.4	0.408	1.17E-04	1.17E+02	47.8	0.083	8.68E-06	8.68E+00	13.3	0.029	1.09E-05	1.09E+01
6-8	565.1	2.9	0.010	1.72E-05	1.72E+01	21.4	0.160	3.74E-05	3.74E+01	32.3	0.053	8.20E-06	8.20E+00	13.2	0.052	1.97E-05	1.97E+01
6-9	654.1	2.8	0.015	2.68E-05	2.68E+01	5.8	0.043	3.71E-05	3.71E+01	60.1	0.117	9.73E-06	9.73E+00	10.2	0.032	1.57E-05	1.57E+01
6-10	606.9	4.5	0.016	1.78E-05	1.78E+01	19.9	0.063	1.58E-05	1.58E+01	26.5	0.036	6.79E-06	6.79E+00	12.2	0.039	1.60E-05	1.60E+01
6-11	649.0	4.9	0.012	1.22E-05	1.22E+01	6.8	0.024	1.76E-05	1.76E+01	12.3	0.015	6.10E-06	6.10E+00	8.2	0.025	1.52E-05	1.52E+01
6-12	488.6	4.6	0.010	1.09E-05	1.09E+01	4.4	0.019	2.16E-05	2.16E+01	47.3	0.086	9.09E-06	9.09E+00	7.1	0.025	1.76E-05	1.76E+01
6-13	611.0	3.8	0.008	1.05E-05	1.05E+01	5.8	0.031	2.67E-05	2.67E+01	36.0	0.060	8.33E-06	8.33E+00	25.4	0.234	4.61E-05	4.61E+01
6-14	483.0	2.7	0.008	1.48E-05	1.48E+01	7.9	0.063	3.99E-05	3.99E+01	53.1	0.057	5.37E-06	5.37E+00	15.3	0.032	1.05E-05	1.05E+01
6-15	555.0	1.2	0.012	5.00E-05	5.00E+01	7.2	0.021	1.46E-05	1.46E+01	58.1	0.102	8.78E-06	8.78E+00	13.2	0.035	1.33E-05	1.33E+01
6-16	521.0	2.4	0.008	1.67E-05	1.67E+01	13.3	0.245	9.21E-05	9.21E+01	47.5	0.060	6.32E-06	6.32E+00	6.1	0.015	1.23E-05	1.23E+01
6-17	537.5	2.5	0.009	1.80E-05	1.80E+01	19.4	0.086	2.22E-05	2.22E+01	49.6	0.084	8.47E-06	8.47E+00	10.1	0.031	1.53E-05	1.53E+01
6-18	459.7	0.8	0.007	4.38E-05	4.38E+01	10.7	0.012	5.61E-06	5.61E+00	31.6	0.023	3.64E-06	3.64E+00	8.3	0.016	9.64E-06	9.64E+00
6-19	640.2	4.5	0.008	8.89E-06	8.89E+00	14.6	0.102	3.49E-05	3.49E+01	47.3	0.070	7.40E-06	7.40E+00	25.1	0.138	2.75E-05	2.75E+01
6-20	568.2	1.0	0.008	4.00E-05	4.00E+01	11.8	0.047	1.99E-05	1.99E+01	39.5	0.047	5.95E-06	5.95E+00	4.1	0.010	1.22E-05	1.22E+01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
7-1	698.6	4.8	0.008	8.33E-06	8.33E+00	9.0	0.016	8.89E-06	8.89E+00	66.5	0.015	1.13E-06	1.13E+00	21.0	0.020	4.76E-06	4.76E+00
7-2	659.7	5.5	0.008	7.27E-06	7.27E+00	16.5	0.080	2.42E-05	2.42E+01	68.3	0.014	1.02E-06	1.02E+00	28.9	0.022	3.81E-06	3.81E+00
7-3	539.2	5.2	0.008	7.69E-06	7.69E+00	9.2	0.010	5.43E-06	5.43E+00	53.5	0.013	1.21E-06	1.21E+00	36.1	0.029	4.02E-06	4.02E+00
7-4	487.2	6.5	0.007	5.38E-06	5.38E+00	20.3	0.104	2.56E-05	2.56E+01	65.6	0.012	9.15E-07	9.15E-01	21.9	0.015	3.42E-06	3.42E+00
7-5	586.6	2.3	0.001	2.17E-06	2.17E+00	19.6	0.018	4.59E-06	4.59E+00	43.5	0.009	1.03E-06	1.03E+00	21.4	0.016	3.74E-06	3.74E+00
7-6	558.7	4.2	0.007	8.33E-06	8.33E+00	12.9	0.034	1.32E-05	1.32E+01	63.4	0.011	8.68E-07	8.68E-01	13.6	0.015	5.51E-06	5.51E+00
7-7	591.2	2.2	0.007	1.59E-05	1.59E+01	20.9	0.015	3.59E-06	3.59E+00	68.7	0.011	8.01E-07	8.01E-01	10.5	0.008	3.81E-06	3.81E+00
7-8	471.3	3.5	0.007	1.00E-05	1.00E+01	11.4	0.011	4.82E-06	4.82E+00	46.9	0.011	1.17E-06	1.17E+00	21.7	0.013	3.00E-06	3.00E+00
7-9	543.4	5.2	0.008	7.69E-06	7.69E+00	12.9	0.104	4.03E-05	4.03E+01	50.4	0.010	9.92E-07	9.92E-01	19.1	0.013	3.40E-06	3.40E+00
7-10	542.7	2.7	0.007	1.30E-05	1.30E+01	14.4	0.023	7.99E-06	7.99E+00	59.1	0.010	8.46E-07	8.46E-01	15.8	0.010	3.16E-06	3.16E+00
7-11	555.8	16.0	0.008	2.50E-06	2.50E+00	11.4	0.014	6.14E-06	6.14E+00	57.2	0.011	9.62E-07	9.62E-01	13.7	0.014	5.11E-06	5.11E+00
7-12	601.8	11.1	0.007	3.15E-06	3.15E+00	17.3	0.008	2.31E-06	2.31E+00	68.8	0.011	7.99E-07	7.99E-01	24.5	0.010	2.04E-06	2.04E+00
7-13	524.7	4.8	0.008	8.33E-06	8.33E+00	8.7	0.009	5.17E-06	5.17E+00	51.5	0.011	1.07E-06	1.07E+00	12.2	0.008	3.28E-06	3.28E+00
7-14	442.4	4.1	0.007	8.54E-06	8.54E+00	6.9	0.008	5.80E-06	5.80E+00	67.8	0.011	8.11E-07	8.11E-01	23.8	0.016	3.36E-06	3.36E+00
7-15	592.3	5.9	0.008	6.78E-06	6.78E+00	19.7	0.038	9.64E-06	9.64E+00	83.5	0.014	8.38E-07	8.38E-01	14.4	0.011	3.82E-06	3.82E+00
7-16	658.6	4.6	0.008	8.70E-06	8.70E+00	20.2	0.021	5.20E-06	5.20E+00	81.5	0.015	9.20E-07	9.20E-01	21.2	0.020	4.72E-06	4.72E+00
7-17	472.5	6.3	0.007	5.56E-06	5.56E+00	5.4	0.008	7.41E-06	7.41E+00	60.5	0.010	8.26E-07	8.26E-01	10.7	0.009	4.21E-06	4.21E+00
7-18	467.8	4.0	0.007	8.75E-06	8.75E+00	7.2	0.013	9.03E-06	9.03E+00	46.4	0.012	1.29E-06	1.29E+00	21.2	0.009	2.12E-06	2.12E+00
7-19	408.7	3.0	0.007	1.17E-05	1.17E+01	7.3	0.007	4.79E-06	4.79E+00	59.0	0.008	6.78E-07	6.78E-01	20.6	0.008	1.94E-06	1.94E+00
7-20	516.9	3.6	0.007	9.72E-06	9.72E+00	6.5	0.008	6.15E-06	6.15E+00	44.6	0.009	1.01E-06	1.01E+00	9.3	0.008	4.30E-06	4.30E+00
8-1	536.8	5.4	0.007	6.48E-06	6.48E+00	6.4	0.008	6.25E-06	6.25E+00	19.2	0.008	2.08E-06	2.08E+00	7.0	0.008	5.71E-06	5.71E+00
8-2	682.7	4.4	0.008	9.09E-06	9.09E+00	9.7	0.012	6.19E-06	6.19E+00	12.3	0.008	3.25E-06	3.25E+00	7.3	0.009	6.16E-06	6.16E+00
8-3	758.6	1.1	0.001	4.55E-06	4.55E+00	7.4	0.009	6.08E-06	6.08E+00	17.3	0.009	2.60E-06	2.60E+00	7.9	0.009	5.70E-06	5.70E+00
8-4	490.7	1.2	0.001	4.17E-06	4.17E+00	3.6	0.008	1.11E-05	1.11E+01	24.4	0.008	1.64E-06	1.64E+00	5.8	0.011	9.48E-06	9.48E+00
8-5	380.2	1.8	0.007	1.94E-05	1.94E+01	5.7	0.008	7.02E-06	7.02E+00	28.5	0.009	1.58E-06	1.58E+00	8.7	0.009	5.17E-06	5.17E+00
8-6	528.4	2.1	0.001	2.38E-06	2.38E+00	5.0	0.009	9.00E-06	9.00E+00	44.7	0.010	1.12E-06	1.12E+00	10.4	0.009	4.33E-06	4.33E+00
8-7	840.8	5.0	0.008	8.00E-06	8.00E+00	20.5	0.009	2.20E-06	2.20E+00	62.5	0.011	8.80E-07	8.80E-01	5.5	0.008	7.27E-06	7.27E+00
8-8	704.8	4.0	0.008	1.00E-05	1.00E+01	6.8	0.010	7.35E-06	7.35E+00	43.5	0.010	1.15E-06	1.15E+00	9.3	0.008	4.30E-06	4.30E+00
8-9	575.6	2.5	0.007	1.40E-05	1.40E+01	8.8	0.009	5.11E-06	5.11E+00	44.7	0.007	7.83E-07	7.83E-01	6.1	0.007	5.74E-06	5.74E+00
8-10	722.1	3.8	0.007	9.21E-06	9.21E+00	5.1	0.008	7.84E-06	7.84E+00	32.5	0.008	1.23E-06	1.23E+00	14.4	0.009	3.13E-06	3.13E+00
8-11	879.0	2.6	0.007	1.35E-05	1.35E+01	12.7	0.001	3.94E-07	3.94E-01	26.8	0.009	1.68E-06	1.68E+00	9.6	0.011	5.73E-06	5.73E+00
8-12	550.8	1.0	0.001	5.00E-06	5.00E+00	8.6	0.008	4.65E-06	4.65E+00	24.6	0.008	1.63E-06	1.63E+00	9.6	0.007	3.65E-06	3.65E+00
8-13	459.9	0.8	0.001	6.25E-06	6.25E+00	3.5	0.007	1.00E-05	1.00E+01	33.1	0.007	1.06E-06	1.06E+00	14.2	0.011	3.87E-06	3.87E+00
8-14	451.1	1.4	0.001	3.57E-06	3.57E+00	6.1	0.007	5.74E-06	5.74E+00	29.3	0.007	1.19E-06	1.19E+00	13.7	0.008	2.92E-06	2.92E+00
8-15	483.2	3.7	0.006	8.11E-06	8.11E+00	4.1	0.006	7.32E-06	7.32E+00	36.4	0.007	9.62E-07	9.62E-01	7.3	0.007	4.79E-06	4.79E+00
8-16	530.7	1.7	0.001	2.94E-06	2.94E+00	5.1	0.006	5.88E-06	5.88E+00	48.6	0.008	8.23E-07	8.23E-01	7.8	0.006	3.85E-06	3.85E+00
8-17	515.3	2.0	0.006	1.50E-05	1.50E+01	7.9	0.008	5.06E-06	5.06E+00	43.2	0.008	9.26E-07	9.26E-01	7.1	0.008	5.63E-06	5.63E+00
8-18	372.9	1.8	0.001	2.78E-06	2.78E+00	3.8	0.006	7.89E-06	7.89E+00	34.4	0.008	1.16E-06	1.16E+00	3.0	0.001	1.67E-06	1.67E+00
8-19	344.0	1.1	0.001	4.55E-06	4.55E+00	5.2	0.006	5.77E-06	5.77E+00	26.2	0.006	1.15E-06	1.15E+00	6.6	0.006	4.55E-06	4.55E+00
8-20	307.0	0.8	0.001	6.25E-06	6.25E+00	3.3	0.001	1.52E-06	1.52E+00	32.7	0.006	9.17E-07	9.17E-01	3.7	0.001	1.35E-06	1.35E+00

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
9-1	648.4	2.0	0.006	1.50E-05	1.50E+01	21.4	0.013	3.04E-06	3.04E+00	11.3	0.006	2.65E-06	2.65E+00	9.1	0.009	4.95E-06	4.95E+00
9-2	604.0	3.9	0.006	7.69E-06	7.69E+00	17.1	0.007	2.05E-06	2.05E+00	9.5	0.006	3.16E-06	3.16E+00	13.0	0.019	7.31E-06	7.31E+00
9-3	548.8	3.1	0.006	9.68E-06	9.68E+00	9.1	0.007	3.85E-06	3.85E+00	11.8	0.006	2.54E-06	2.54E+00	3.2	0.007	1.09E-05	1.09E+01
9-4	561.9	1.8	0.006	1.67E-05	1.67E+01	6.2	0.008	6.45E-06	6.45E+00	13.0	0.006	2.31E-06	2.31E+00	4.6	0.001	1.09E-06	1.09E+00
9-5	628.3	4.0	0.006	7.50E-06	7.50E+00	11.5	0.010	4.35E-06	4.35E+00	23.3	0.006	1.29E-06	1.29E+00	7.6	0.006	3.95E-06	3.95E+00
9-6	524.4	3.6	0.006	8.33E-06	8.33E+00	12.2	0.034	1.39E-05	1.39E+01	59.9	0.009	7.51E-07	7.51E-01	23.7	0.013	2.74E-06	2.74E+00
9-7	461.5	2.7	0.001	1.85E-06	1.85E+00	7.7	0.007	4.55E-06	4.55E+00	45.6	0.007	7.68E-07	7.68E-01	11.0	0.010	4.55E-06	4.55E+00
9-8	557.4	1.1	0.001	4.55E-06	4.55E+00	16.6	0.007	2.11E-06	2.11E+00	45.4	0.007	7.71E-07	7.71E-01	18.1	0.009	2.49E-06	2.49E+00
9-9	325.7	3.1	0.006	9.68E-06	9.68E+00	8.5	0.009	5.29E-06	5.29E+00	51.3	0.008	7.80E-07	7.80E-01	28.3	0.011	1.94E-06	1.94E+00
9-10	454.1	1.1	0.006	2.73E-05	2.73E+01	7.1	0.001	7.04E-07	7.04E-01	43.2	0.007	8.10E-07	8.10E-01	5.6	0.001	8.93E-07	8.93E-01
9-11	487.9	1.8	0.001	2.78E-06	2.78E+00	10.4	0.008	3.85E-06	3.85E+00	43.6	0.006	6.88E-07	6.88E-01	14.1	0.006	2.13E-06	2.13E+00
9-12	483.5	4.9	0.006	6.12E-06	6.12E+00	12.6	0.008	3.17E-06	3.17E+00	65.8	0.009	6.84E-07	6.84E-01	25.1	0.010	1.99E-06	1.99E+00
9-13	500.0	5.1	0.006	5.88E-06	5.88E+00	9.8	0.009	4.59E-06	4.59E+00	59.4	0.010	8.42E-07	8.42E-01	17.3	0.013	3.76E-06	3.76E+00
9-14	582.8	5.2	0.006	5.77E-06	5.77E+00	10.4	0.010	4.81E-06	4.81E+00	81.5	0.012	7.36E-07	7.36E-01	17.9	0.026	7.26E-06	7.26E+00
9-15	478.8	4.1	0.006	7.32E-06	7.32E+00	7.4	0.007	4.73E-06	4.73E+00	59.2	0.008	6.76E-07	6.76E-01	19.4	0.010	2.58E-06	2.58E+00
9-16	523.7	4.8	0.006	6.25E-06	6.25E+00	17.2	0.010	2.91E-06	2.91E+00	80.6	0.011	6.82E-07	6.82E-01	15.5	0.009	2.90E-06	2.90E+00
9-17	666.6	7.1	0.006	4.23E-06	4.23E+00	13.9	0.009	3.24E-06	3.24E+00	90.5	0.013	7.18E-07	7.18E-01	19.7	0.013	3.30E-06	3.30E+00
9-18	559.7	7.5	0.007	4.67E-06	4.67E+00	6.8	0.008	5.88E-06	5.88E+00	75.1	0.011	7.32E-07	7.32E-01	16.8	0.010	2.98E-06	2.98E+00
9-19	619.1	2.1	0.001	2.38E-06	2.38E+00	15.2	0.019	6.25E-06	6.25E+00	93.7	0.013	6.94E-07	6.94E-01	19.8	0.011	2.78E-06	2.78E+00
9-20	528.1	4.7	0.007	7.45E-06	7.45E+00	10.8	0.009	4.17E-06	4.17E+00	64.5	0.010	7.75E-07	7.75E-01	26.5	0.020	3.77E-06	3.77E+00
10-1	507.4	2.3	0.009	1.96E-05	1.96E+01	11.7	0.108	4.62E-05	4.62E+01	34.9	0.028	4.01E-06	4.01E+00	19.8	0.046	1.16E-05	1.16E+01
10-2	686.6	8.4	0.012	7.14E-06	7.14E+00	27.2	0.149	2.74E-05	2.74E+01	66.2	0.073	5.51E-06	5.51E+00	20.6	0.044	1.07E-05	1.07E+01
10-3	588.6	2.6	0.008	1.54E-05	1.54E+01	36.9	0.300	4.07E-05	4.07E+01	37.1	0.034	4.58E-06	4.58E+00	24.6	0.088	1.79E-05	1.79E+01
10-4	621.7	4.3	0.011	1.28E-05	1.28E+01	23.3	0.129	2.77E-05	2.77E+01	44.5	0.059	6.63E-06	6.63E+00	27.9	0.162	2.90E-05	2.90E+01
10-5	553.5	1.5	0.008	2.67E-05	2.67E+01	20.5	0.033	8.05E-06	8.05E+00	37.2	0.036	4.84E-06	4.84E+00	26.7	0.140	2.62E-05	2.62E+01
10-6	479.6	2.5	0.011	2.20E-05	2.20E+01	8.5	0.014	8.24E-06	8.24E+00	45.9	0.043	4.68E-06	4.68E+00	26.4	0.037	7.01E-06	7.01E+00
10-7	683.6	5.7	0.010	8.77E-06	8.77E+00	12.6	0.050	1.98E-05	1.98E+01	53.7	0.047	4.38E-06	4.38E+00	32.1	0.084	1.31E-05	1.31E+01
10-8	714.2	3.5	0.009	1.29E-05	1.29E+01	9.5	0.022	1.16E-05	1.16E+01	70.5	0.056	3.97E-06	3.97E+00	26.7	0.096	1.80E-05	1.80E+01
10-9	553.2	3.4	0.010	1.47E-05	1.47E+01	7.5	0.016	1.07E-05	1.07E+01	53.4	0.031	2.90E-06	2.90E+00	27.8	0.032	5.76E-06	5.76E+00
10-10	583.0	3.0	0.011	1.83E-05	1.83E+01	6.8	0.014	1.03E-05	1.03E+01	41.8	0.031	3.71E-06	3.71E+00	27.9	0.083	1.49E-05	1.49E+01
10-11	641.2	5.1	0.012	1.18E-05	1.18E+01	29.2	0.069	1.18E-05	1.18E+01	57.2	0.059	5.16E-06	5.16E+00	37.4	0.091	1.22E-05	1.22E+01
10-12	562.5	5.4	0.014	1.30E-05	1.30E+01	24.2	0.110	2.27E-05	2.27E+01	67.3	0.074	5.50E-06	5.50E+00	24.3	0.094	1.93E-05	1.93E+01
10-13	390.1	3.1	0.008	1.29E-05	1.29E+01	51.3	0.050	4.87E-06	4.87E+00	33.9	0.025	3.69E-06	3.69E+00	30.5	0.075	1.23E-05	1.23E+01
10-14	535.3	2.8	0.008	1.43E-05	1.43E+01	12.0	0.034	1.42E-05	1.42E+01	62.4	0.050	4.01E-06	4.01E+00	33.9	0.081	1.19E-05	1.19E+01
10-15	636.9	7.1	0.013	9.15E-06	9.15E+00	14.0	0.017	6.07E-06	6.07E+00	65.0	0.060	4.62E-06	4.62E+00	33.4	0.087	1.30E-05	1.30E+01
10-16	409.0	2.7	0.009	1.67E-05	1.67E+01	11.8	0.026	1.10E-05	1.10E+01	47.4	0.036	3.80E-06	3.80E+00	19.3	0.050	1.30E-05	1.30E+01
10-17	462.1	3.8	0.008	1.05E-05	1.05E+01	11.4	0.024	1.05E-05	1.05E+01	73.1	0.056	3.83E-06	3.83E+00	32.5	0.056	8.62E-06	8.62E+00
10-18	501.0	4.0	0.010	1.25E-05	1.25E+01	20.4	0.024	5.88E-06	5.88E+00	46.6	0.033	3.54E-06	3.54E+00	51.6	0.111	1.08E-05	1.08E+01
10-19	458.1	3.5	0.010	1.43E-05	1.43E+01	18.4	0.055	1.49E-05	1.49E+01	60.9	0.048	3.94E-06	3.94E+00	17.1	0.011	3.22E-06	3.22E+00
10-20	443.2	3.6	0.008	1.11E-05	1.11E+01	8.1	0.009	5.56E-06	5.56E+00	61.9	0.028	2.26E-06	2.26E+00	27.3	0.064	1.17E-05	1.17E+01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
11-1	777.6	6.7	0.010	7.46E-06	7.46E+00	25.2	0.074	1.47E-05	1.47E+01	78.1	0.045	2.88E-06	2.88E+00	43.1	0.097	1.13E-05	1.13E+01
11-2	769.7	12.1	0.053	2.19E-05	2.19E+01	24.7	0.013	2.63E-06	2.63E+00	73.8	0.036	2.44E-06	2.44E+00	35.9	0.081	1.13E-05	1.13E+01
11-3	523.3	2.4	0.038	7.92E-05	7.92E+01	21.0	0.019	4.52E-06	4.52E+00	31.7	0.011	1.74E-06	1.74E+00	19.5	0.012	3.08E-06	3.08E+00
11-4	781.6	9.3	0.009	4.84E-06	4.84E+00	28.9	0.026	4.50E-06	4.50E+00	51.0	0.021	2.06E-06	2.06E+00	39.2	0.078	9.95E-06	9.95E+00
11-5	564.6	3.2	0.004	6.25E-06	6.25E+00	27.7	0.040	7.22E-06	7.22E+00	42.5	0.020	2.35E-06	2.35E+00	28.7	0.084	1.46E-05	1.46E+01
11-6	524.3	3.5	0.004	5.71E-06	5.71E+00	8.4	0.046	2.74E-05	2.74E+01	44.9	0.019	2.12E-06	2.12E+00	18.2	0.057	1.57E-05	1.57E+01
11-7	529.6	3.4	0.005	7.35E-06	7.35E+00	26.2	0.115	2.19E-05	2.19E+01	36.6	0.014	1.91E-06	1.91E+00	26.8	0.050	9.33E-06	9.33E+00
11-8	407.8	3.1	0.004	6.45E-06	6.45E+00	11.5	0.041	1.78E-05	1.78E+01	33.3	0.013	1.95E-06	1.95E+00	16.9	0.011	3.25E-06	3.25E+00
11-9	573.2	3.4	0.004	5.88E-06	5.88E+00	13.0	0.019	7.31E-06	7.31E+00	41.3	0.014	1.69E-06	1.69E+00	28.5	0.027	4.74E-06	4.74E+00
11-10	458.7	1.8	0.003	8.33E-06	8.33E+00	12.3	0.007	2.85E-06	2.85E+00	45.9	0.017	1.85E-06	1.85E+00	30.3	0.054	8.91E-06	8.91E+00
11-11	628.2	5.7	0.007	6.14E-06	6.14E+00	13.4	0.025	9.33E-06	9.33E+00	77.4	0.033	2.13E-06	2.13E+00	58.4	0.115	9.85E-06	9.85E+00
11-12	657.5	6.3	0.007	5.56E-06	5.56E+00	14.8	0.016	5.41E-06	5.41E+00	65.6	0.040	3.05E-06	3.05E+00	24.6	0.049	9.96E-06	9.96E+00
11-13	637.7	6.3	0.006	4.76E-06	4.76E+00	17.5	0.023	6.57E-06	6.57E+00	65.8	0.038	2.89E-06	2.89E+00	23.2	0.070	1.51E-05	1.51E+01
11-14	442.7	none				6.2	0.026	2.10E-05	2.10E+01	47.2	0.025	2.65E-06	2.65E+00	23.7	0.048	1.01E-05	1.01E+01
11-15	647.1	3.5	0.004	5.71E-06	5.71E+00	8.5	0.009	5.29E-06	5.29E+00	71.0	0.033	2.32E-06	2.32E+00	46.6	0.091	9.76E-06	9.76E+00
11-16	512.7	1.9	0.004	1.05E-05	1.05E+01	9.2	0.009	4.89E-06	4.89E+00	49.9	0.022	2.20E-06	2.20E+00	38.7	0.076	9.82E-06	9.82E+00
11-17	509.7	6.7	0.006	4.48E-06	4.48E+00	15.9	0.028	8.81E-06	8.81E+00	54.9	0.029	2.64E-06	2.64E+00	18.8	0.022	5.85E-06	5.85E+00
11-18	502.3	6.3	0.006	4.76E-06	4.76E+00	16.7	0.066	1.98E-05	1.98E+01	53.4	0.022	2.06E-06	2.06E+00	33.3	0.066	9.91E-06	9.91E+00
11-19	575.9	5.3	0.005	4.72E-06	4.72E+00	21.5	0.012	2.79E-06	2.79E+00	42.8	0.015	1.75E-06	1.75E+00	47.7	0.063	6.60E-06	6.60E+00
11-20	654.9	6.7	0.006	4.48E-06	4.48E+00	22.3	0.101	2.26E-05	2.26E+01	71.5	0.027	1.89E-06	1.89E+00	34.9	0.058	8.31E-06	8.31E+00
12-1	724.4	3.0	0.005	8.33E-06	8.33E+00	13.2	0.011	4.17E-06	4.17E+00	26.6	0.015	2.82E-06	2.82E+00	4.3	0.005	5.81E-06	5.81E+00
12-2	690.8	1.2	0.005	2.08E-05	2.08E+01	16.2	0.045	1.39E-05	1.39E+01	43.6	0.039	4.47E-06	4.47E+00	10.6	0.009	4.25E-06	4.25E+00
12-3	784.0	6.1	0.005	4.10E-06	4.10E+00	16.5	0.023	6.97E-06	6.97E+00	39.3	0.027	3.44E-06	3.44E+00	14.4	0.020	6.94E-06	6.94E+00
12-4	733.2	4.1	0.006	7.32E-06	7.32E+00	17.6	0.024	6.82E-06	6.82E+00	44.5	0.032	3.60E-06	3.60E+00	19.0	0.031	8.16E-06	8.16E+00
12-5	771.3	1.3	0.004	1.54E-05	1.54E+01	12.4	0.023	9.27E-06	9.27E+00	49.3	0.041	4.16E-06	4.16E+00	16.3	0.030	9.20E-06	9.20E+00
12-6	517.3	2.2	0.005	1.14E-05	1.14E+01	9.4	0.009	4.79E-06	4.79E+00	49.2	0.038	3.86E-06	3.86E+00	8.1	0.008	4.94E-06	4.94E+00
12-7	761.4	3.4	0.005	7.35E-06	7.35E+00	17.6	0.054	1.53E-05	1.53E+01	44.5	0.033	3.71E-06	3.71E+00	17.1	0.029	8.48E-06	8.48E+00
12-8	457.8	2.8	0.004	7.14E-06	7.14E+00	3.5	0.006	8.57E-06	8.57E+00	37.2	0.021	2.82E-06	2.82E+00	16.2	0.029	8.95E-06	8.95E+00
12-9	655.1	3.8	0.005	6.58E-06	6.58E+00	12.9	0.014	5.43E-06	5.43E+00	46.5	0.026	2.80E-06	2.80E+00	9.8	0.006	3.06E-06	3.06E+00
12-10	603.0	3.2	0.004	6.25E-06	6.25E+00	16.2	0.025	7.72E-06	7.72E+00	41.2	0.023	2.79E-06	2.79E+00	17.0	0.014	4.12E-06	4.12E+00
12-11	517.2	1.2	0.004	1.67E-05	1.67E+01	18.1	0.053	1.46E-05	1.46E+01	35.1	0.019	2.71E-06	2.71E+00	10.2	0.018	8.82E-06	8.82E+00
12-12	533.3	2.1	0.004	9.52E-06	9.52E+00	11.0	0.026	1.18E-05	1.18E+01	48.1	0.034	3.53E-06	3.53E+00	6.6	0.012	9.09E-06	9.09E+00
12-13	469.0	1.1	0.003	1.36E-05	1.36E+01	12.8	0.012	4.69E-06	4.69E+00	29.6	0.016	2.70E-06	2.70E+00	14.6	0.022	7.53E-06	7.53E+00
12-14	597.1	1.2	0.004	1.67E-05	1.67E+01	6.0	0.012	1.00E-05	1.00E+01	64.8	0.045	3.47E-06	3.47E+00	15.3	0.025	8.17E-06	8.17E+00
12-15	553.2	1.7	0.004	1.18E-05	1.18E+01	9.7	0.010	5.15E-06	5.15E+00	44.8	0.020	2.23E-06	2.23E+00	12.6	0.009	3.57E-06	3.57E+00
12-16	574.5	1.4	0.004	1.43E-05	1.43E+01	13.8	0.028	1.01E-05	1.01E+01	80.8	0.059	3.65E-06	3.65E+00	9.9	0.015	7.58E-06	7.58E+00
12-17	683.7	3.8	0.004	5.26E-06	5.26E+00	12.7	0.015	5.91E-06	5.91E+00	53.9	0.030	2.78E-06	2.78E+00	6.5	0.008	6.15E-06	6.15E+00
12-18	638.6	1.5	0.003	1.00E-05	1.00E+01	12.5	0.018	7.20E-06	7.20E+00	35.7	0.021	2.94E-06	2.94E+00	4.7	0.005	5.32E-06	5.32E+00
12-19	515.6	4.9	0.006	6.12E-06	6.12E+00	6.1	0.009	7.38E-06	7.38E+00	59.8	0.045	3.76E-06	3.76E+00	32.4	0.120	1.85E-05	1.85E+01
12-20	543.4	3.6	0.005	6.94E-06	6.94E+00	10.7	0.008	3.74E-06	3.74E+00	54.9	0.030	2.73E-06	2.73E+00	26.3	0.061	1.16E-05	1.16E+01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
13-1	663.9	1.2	0.003	1.25E-05	1.25E+01	4.0	0.001	1.25E-06	1.25E+00	15.9	0.001	3.14E-07	3.14E-01	25.8	0.001	1.94E-07	1.94E-01
13-2	564.8	5.1	0.001	9.80E-07	9.80E-01	19.9	0.001	2.51E-07	2.51E-01	16.3	0.001	3.07E-07	3.07E-01	13.7	0.001	3.65E-07	3.65E-01
13-3	675.6	3.2	0.001	1.56E-06	1.56E+00	8.9	0.001	5.62E-07	5.62E-01	35.2	0.001	1.42E-07	1.42E-01	2.4	0.001	2.08E-06	2.08E+00
13-4	596.4	1.0	0.001	5.00E-06	5.00E+00	8.6	0.001	5.81E-07	5.81E-01	20.8	0.001	2.40E-07	2.40E-01	13.6	0.001	3.68E-07	3.68E-01
13-5	594.4	1.0	0.001	5.00E-06	5.00E+00	4.0	0.001	1.25E-06	1.25E+00	41.4	0.001	1.21E-07	1.21E-01	5.7	0.001	8.77E-07	8.77E-01
13-6	575.4	2.3	0.001	2.17E-06	2.17E+00	6.7	0.001	7.46E-07	7.46E-01	25.5	0.001	1.96E-07	1.96E-01	8.4	0.001	5.95E-07	5.95E-01
13-7	547.3	4.8	0.001	1.04E-06	1.04E+00	7.2	0.001	6.94E-07	6.94E-01	35.9	0.001	1.39E-07	1.39E-01	6.3	0.001	7.94E-07	7.94E-01
13-8	821.5	5.0	0.001	1.00E-06	1.00E+00	10.5	0.001	4.76E-07	4.76E-01	17.2	0.001	2.91E-07	2.91E-01	9.2	0.001	5.43E-07	5.43E-01
13-9	580.5	1.7	0.001	2.94E-06	2.94E+00	9.5	0.001	5.26E-07	5.26E-01	23.3	0.001	2.15E-07	2.15E-01	9.8	0.001	5.10E-07	5.10E-01
13-10	659.5	2.2	0.001	2.27E-06	2.27E+00	21.6	0.001	2.31E-07	2.31E-01	14.9	0.008	2.68E-06	2.68E+00	10.2	0.001	4.90E-07	4.90E-01
13-11	654.5	2.5	0.001	2.00E-06	2.00E+00	7.3	0.001	6.85E-07	6.85E-01	25.1	0.001	1.99E-07	1.99E-01	17.2	0.001	2.91E-07	2.91E-01
13-12	522.4	2.7	0.001	1.85E-06	1.85E+00	8.2	0.001	6.10E-07	6.10E-01	12.2	0.001	4.10E-07	4.10E-01	5.0	0.001	1.00E-06	1.00E+00
13-13	555.9	3.5	0.001	1.43E-06	1.43E+00	5.7	0.001	8.77E-07	8.77E-01	24.3	0.001	2.06E-07	2.06E-01	10.7	0.001	4.67E-07	4.67E-01
13-14	692.4	6.3	0.001	7.94E-07	7.94E-01	11.8	0.001	4.24E-07	4.24E-01	29.0	0.001	1.72E-07	1.72E-01	11.3	0.001	4.42E-07	4.42E-01
13-15	714.7	3.2	0.001	1.56E-06	1.56E+00	9.1	0.001	5.49E-07	5.49E-01	22.8	0.001	2.19E-07	2.19E-01	7.4	0.001	6.76E-07	6.76E-01
13-16	623.3	1.2	0.001	4.17E-06	4.17E+00	8.4	0.001	5.95E-07	5.95E-01	22.9	0.001	2.18E-07	2.18E-01	5.6	0.001	8.93E-07	8.93E-01
13-17	630.5	3.6	0.001	1.39E-06	1.39E+00	4.8	0.001	1.04E-06	1.04E+00	27.8	0.001	1.80E-07	1.80E-01	19.1	0.001	2.62E-07	2.62E-01
13-18	542.0	2.6	0.001	1.92E-06	1.92E+00	8.7	0.001	5.75E-07	5.75E-01	15.5	0.001	3.23E-07	3.23E-01	5.6	0.001	8.93E-07	8.93E-01
13-19	533.4	2.0	0.001	2.50E-06	2.50E+00	11.5	0.001	4.35E-07	4.35E-01	25.7	0.001	1.95E-07	1.95E-01	10.7	0.001	4.67E-07	4.67E-01
13-20	646.1	2.2	0.001	2.27E-06	2.27E+00	9.1	0.001	5.49E-07	5.49E-01	31.7	0.001	1.58E-07	1.58E-01	15.5	0.001	3.23E-07	3.23E-01
14-1	767.8	1.5	0.006	2.00E-05	2.00E+01	18.0	0.006	1.67E-06	1.67E+00	12.0	0.001	4.17E-07	4.17E-01	11.4	0.001	4.39E-07	4.39E-01
14-2	663.9	1.9	0.001	2.63E-06	2.63E+00	14.1	0.001	3.55E-07	3.55E-01	22.5	0.001	2.22E-07	2.22E-01	7.5	0.001	6.67E-07	6.67E-01
14-3	631.5	4.1	0.001	1.22E-06	1.22E+00	8.8	0.001	5.68E-07	5.68E-01	10.8	0.001	4.63E-07	4.63E-01	15.9	0.001	3.14E-07	3.14E-01
14-4	570.0	1.3	0.001	3.85E-06	3.85E+00	20.3	0.001	2.46E-07	2.46E-01	15.4	0.001	3.25E-07	3.25E-01	12.1	0.001	4.13E-07	4.13E-01
14-5	696.0	6.4	0.001	7.81E-07	7.81E-01	19.5	0.001	2.56E-07	2.56E-01	32.7	0.001	1.53E-07	1.53E-01	13.8	0.001	3.62E-07	3.62E-01
14-6	646.4	3.5	0.001	1.43E-06	1.43E+00	17.9	0.001	2.79E-07	2.79E-01	62.2	0.001	8.04E-08	8.04E-02	16.6	0.001	3.01E-07	3.01E-01
14-7	508.9	1.9	0.001	2.63E-06	2.63E+00	10.4	0.001	4.81E-07	4.81E-01	50.1	0.001	9.98E-08	9.98E-02	31.9	0.001	1.57E-07	1.57E-01
14-8	417.4	1.7	0.001	2.94E-06	2.94E+00	12.5	0.001	4.00E-07	4.00E-01	37.1	0.001	1.35E-07	1.35E-01	12.7	0.001	3.94E-07	3.94E-01
14-9	460.8	2.7	0.001	1.85E-06	1.85E+00	8.9	0.001	5.62E-07	5.62E-01	43.2	0.001	1.16E-07	1.16E-01	11.2	0.001	4.46E-07	4.46E-01
14-10	561.2	1.7	0.001	2.94E-06	2.94E+00	7.4	0.001	6.76E-07	6.76E-01	51.1	0.001	9.78E-08	9.78E-02	7.6	0.001	6.58E-07	6.58E-01
14-11	601.2	2.7	0.001	1.85E-06	1.85E+00	7.0	0.001	7.14E-07	7.14E-01	12.3	0.001	4.07E-07	4.07E-01	9.8	0.001	5.10E-07	5.10E-01
14-12	734.4	3.3	0.001	1.52E-06	1.52E+00	8.8	0.001	5.68E-07	5.68E-01	20.0	0.001	2.50E-07	2.50E-01	6.9	0.001	7.25E-07	7.25E-01
14-13	587.2	2.3	0.001	2.17E-06	2.17E+00	18.3	0.001	2.73E-07	2.73E-01	14.4	0.001	3.47E-07	3.47E-01	6.5	0.001	7.69E-07	7.69E-01
14-14	581.4	1.4	0.001	3.57E-06	3.57E+00	12.7	0.001	3.94E-07	3.94E-01	8.4	0.001	5.95E-07	5.95E-01	5.2	0.001	9.62E-07	9.62E-01
14-15	519.8	2.7	0.003	5.56E-06	5.56E+00	6.2	0.001	8.06E-07	8.06E-01	63.7	0.001	7.85E-08	7.85E-02	28.6	0.001	1.75E-07	1.75E-01
14-16	434.0	1.1	0.001	4.55E-06	4.55E+00	5.4	0.001	9.26E-07	9.26E-01	38.1	0.001	1.31E-07	1.31E-01	4.3	0.001	1.16E-06	1.16E+00
14-17	447.8	1.4	0.001	3.57E-06	3.57E+00	14.6	0.001	3.42E-07	3.42E-01	37.3	0.001	1.34E-07	1.34E-01	22.5	0.001	2.22E-07	2.22E-01
14-18	519.7	4.9	0.001	1.02E-06	1.02E+00	12.2	0.001	4.10E-07	4.10E-01	72.6	0.001	6.89E-08	6.89E-02	13.5	0.001	3.70E-07	3.70E-01
14-19	586.3	3.8	0.001	1.32E-06	1.32E+00	11.3	0.001	4.42E-07	4.42E-01	59.4	0.001	8.42E-08	8.42E-02	12.8	0.001	3.91E-07	3.91E-01
14-20	852.2	7.2	0.001	6.94E-07	6.94E-01	14.5	0.001	3.45E-07	3.45E-01	96.1	0.001	5.20E-08	5.20E-02	23.0	0.001	2.17E-07	2.17E-01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
15-1	486.0	2.7	0.001	1.85E-06	1.85E+00	2.8	0.001	1.79E-06	1.79E+00	12.8	0.001	3.91E-07	3.91E-01	none	0.001		
15-2	464.0	3.1	0.001	1.61E-06	1.61E+00	2.7	0.001	1.85E-06	1.85E+00	12.4	0.001	4.03E-07	4.03E-01	2.6	0.001	1.92E-06	1.92E+00
15-3	493.0	2.9	0.001	1.72E-06	1.72E+00	6.2	0.001	8.06E-07	8.06E-01	13.8	0.001	3.62E-07	3.62E-01	1.5	0.001	3.33E-06	3.33E+00
15-4	430.0	1.1	0.001	4.55E-06	4.55E+00	0.1	0.001	5.00E-05	5.00E+01	15.7	0.001	3.18E-07	3.18E-01	3.9	0.001	1.28E-06	1.28E+00
15-5	834.0	2.5	0.001	2.00E-06	2.00E+00	6.5	0.001	7.69E-07	7.69E-01	14.1	0.001	3.55E-07	3.55E-01	9.8	0.001	5.10E-07	5.10E-01
15-6	406.0	2.0	0.001	2.50E-06	2.50E+00	4.3	0.001	1.16E-06	1.16E+00	13.2	0.001	3.79E-07	3.79E-01	6.4	0.001	7.81E-07	7.81E-01
15-7	671.0	0.9	0.001	5.56E-06	5.56E+00	8.7	0.001	5.75E-07	5.75E-01	19.7	0.001	2.54E-07	2.54E-01	1.7	0.001	2.94E-06	2.94E+00
15-8	613.0	1.2	0.001	4.17E-06	4.17E+00	7.9	0.001	6.33E-07	6.33E-01	14.5	0.001	3.45E-07	3.45E-01	8.1	0.001	6.17E-07	6.17E-01
15-9	606.0	2.5	0.001	2.00E-06	2.00E+00	12.2	0.001	4.10E-07	4.10E-01	14.5	0.001	3.45E-07	3.45E-01	3.2	0.001	1.56E-06	1.56E+00
15-10	512.0	2.6	0.001	1.92E-06	1.92E+00	11.7	0.001	4.27E-07	4.27E-01	20.7	0.001	2.42E-07	2.42E-01	5.3	0.001	9.43E-07	9.43E-01
15-11	432.0	3.6	0.001	1.39E-06	1.39E+00	8.0	0.001	6.25E-07	6.25E-01	28.5	0.001	1.75E-07	1.75E-01	3.5	0.001	1.43E-06	1.43E+00
15-12	609.0	1.1	0.001	4.55E-06	4.55E+00	5.8	0.001	8.62E-07	8.62E-01	16.5	0.001	3.03E-07	3.03E-01	5.0	0.001	1.00E-06	1.00E+00
15-13	601.0	0.7	0.001	7.14E-06	7.14E+00	8.5	0.001	5.88E-07	5.88E-01	14.6	0.001	3.42E-07	3.42E-01	11.8	0.001	4.24E-07	4.24E-01
15-14	542.0	2.1	0.001	2.38E-06	2.38E+00	4.0	0.001	1.25E-06	1.25E+00	53.7	0.001	9.31E-08	9.31E-02	23.6	0.001	2.12E-07	2.12E-01
15-15	528.0	1.9	0.001	2.63E-06	2.63E+00	4.3	0.001	1.16E-06	1.16E+00	19.7	0.001	2.54E-07	2.54E-01	4.3	0.001	1.16E-06	1.16E+00
15-16	435.0	1.7	0.001	2.94E-06	2.94E+00	3.4	0.001	1.47E-06	1.47E+00	26.9	0.001	1.86E-07	1.86E-01	3.2	0.001	1.56E-06	1.56E+00
15-17	590.0	4.1	0.001	1.22E-06	1.22E+00	5.6	0.001	8.93E-07	8.93E-01	20.1	0.001	2.49E-07	2.49E-01	5.6	0.001	8.93E-07	8.93E-01
15-18	517.1	5.7	0.001	8.77E-07	8.77E-01	10.4	0.001	4.81E-07	4.81E-01	3.2	0.001	1.56E-06	1.56E+00	61.6	0.001	8.12E-08	8.12E-02
15-19	411.9	2.9	0.001	1.72E-06	1.72E+00	4.3	0.001	1.16E-06	1.16E+00	71.0	0.001	7.04E-08	7.04E-02	9.9	0.001	5.05E-07	5.05E-01
15-20	609.3	9.0	0.001	5.56E-07	5.56E-01	16.3	0.001	3.07E-07	3.07E-01	68.3	0.001	7.32E-08	7.32E-02	29.1	0.001	1.72E-07	1.72E-01
16-1	479.0	4.3	0.001	1.16E-06	1.16E+00	5.4	0.001	9.26E-07	9.26E-01	23.1	0.001	2.16E-07	2.16E-01	7.8	0.001	6.41E-07	6.41E-01
16-2	525.1	3.8	0.001	1.32E-06	1.32E+00	7.4	0.001	6.76E-07	6.76E-01	43.4	0.001	1.15E-07	1.15E-01	14.0	0.001	3.57E-07	3.57E-01
16-3	529.3	3.1	0.001	1.61E-06	1.61E+00	9.0	0.001	5.56E-07	5.56E-01	40.7	0.001	1.23E-07	1.23E-01	6.3	0.001	7.94E-07	7.94E-01
16-4	447.1	3.5	0.001	1.43E-06	1.43E+00	0.9	0.001	5.56E-06	5.56E+00	36.8	0.001	1.36E-07	1.36E-01	12.3	0.001	4.07E-07	4.07E-01
16-5	550.1	1.8	0.001	2.78E-06	2.78E+00	8.8	0.001	5.68E-07	5.68E-01	39.3	0.001	1.27E-07	1.27E-01	7.8	0.001	6.41E-07	6.41E-01
16-6	699.2	3.8	0.001	1.32E-06	1.32E+00	11.9	0.001	4.20E-07	4.20E-01	45.7	0.001	1.09E-07	1.09E-01	25.4	0.001	1.97E-07	1.97E-01
16-7	609.1	6.0	0.001	8.33E-07	8.33E-01	7.9	0.001	6.33E-07	6.33E-01	40.6	0.001	1.23E-07	1.23E-01	16.8	0.001	2.98E-07	2.98E-01
16-8	467.3	2.2	0.001	2.27E-06	2.27E+00	7.8	0.001	6.41E-07	6.41E-01	34.9	0.001	1.43E-07	1.43E-01	11.7	0.001	4.27E-07	4.27E-01
16-9	493.3	2.1	0.001	2.38E-06	2.38E+00	8.6	0.001	5.81E-07	5.81E-01	22.2	0.001	2.25E-07	2.25E-01	7.0	0.001	7.14E-07	7.14E-01
16-10	551.0	3.2	0.001	1.56E-06	1.56E+00	5.9	0.001	8.47E-07	8.47E-01	39.4	0.001	1.27E-07	1.27E-01	9.4	0.001	5.32E-07	5.32E-01
16-11	526.0	2.6	0.001	1.92E-06	1.92E+00	7.9	0.001	6.33E-07	6.33E-01	49.7	0.001	1.01E-07	1.01E-01	15.1	0.001	3.31E-07	3.31E-01
16-12	461.0	0.9	0.001	5.56E-06	5.56E+00	10.0	0.001	5.00E-07	5.00E-01	26.9	0.001	1.86E-07	1.86E-01	11.4	0.001	4.39E-07	4.39E-01
16-13	413.6	1.5	0.001	3.33E-06	3.33E+00	11.5	0.001	4.35E-07	4.35E-01	43.7	0.001	1.14E-07	1.14E-01	23.3	0.001	2.15E-07	2.15E-01
16-14	507.3	4.2	0.001	1.19E-06	1.19E+00	10.7	0.001	4.67E-07	4.67E-01	32.6	0.001	1.53E-07	1.53E-01	6.0	0.001	8.33E-07	8.33E-01
16-15	491.7	1.0	0.001	5.00E-06	5.00E+00	10.6	0.001	4.72E-07	4.72E-01	37.1	0.001	1.35E-07	1.35E-01	8.8	0.001	5.68E-07	5.68E-01
16-16	549.6	1.3	0.001	3.85E-06	3.85E+00	6.2	0.001	8.06E-07	8.06E-01	38.5	0.001	1.30E-07	1.30E-01	13.1	0.001	3.82E-07	3.82E-01
16-17	477.7	3.4	0.001	1.47E-06	1.47E+00	11.6	0.001	4.31E-07	4.31E-01	23.5	0.001	2.13E-07	2.13E-01	22.1	0.001	2.26E-07	2.26E-01
16-18	577.8	4.4	0.001	1.14E-06	1.14E+00	9.8	0.001	5.10E-07	5.10E-01	44.8	0.001	1.12E-07	1.12E-01	13.9	0.001	3.60E-07	3.60E-01
16-19	466.1	4.6	0.001	1.09E-06	1.09E+00	3.9	0.001	1.28E-06	1.28E+00	44.3	0.001	1.13E-07	1.13E-01	10.0	0.001	5.00E-07	5.00E-01
16-20	501.4	3.2	0.001	1.56E-06	1.56E+00	11.7	0.001	4.27E-07	4.27E-01	44.1	0.001	1.13E-07	1.13E-01	7.7	0.001	6.49E-07	6.49E-01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
17-1	638.3	6.4	0.001	7.81E-07	7.81E-01	15.2	0.001	3.29E-07	3.29E-01	55.2	0.001	9.06E-08	9.06E-02	26.2	0.001	1.91E-07	1.91E-01
17-2	466.2	3.7	0.001	1.35E-06	1.35E+00	9.2	0.001	5.43E-07	5.43E-01	49.7	0.001	1.01E-07	1.01E-01	34.5	0.001	1.45E-07	1.45E-01
17-3	604.3	6.4	0.001	7.81E-07	7.81E-01	19.3	0.001	2.59E-07	2.59E-01	64.5	0.001	7.75E-08	7.75E-02	16.6	0.001	3.01E-07	3.01E-01
17-4	647.2	6.1	0.001	8.20E-07	8.20E-01	20.3	0.001	2.46E-07	2.46E-01	63.5	0.001	7.87E-08	7.87E-02	36.3	0.001	1.38E-07	1.38E-01
17-5	555.9	2.8	0.001	1.79E-06	1.79E+00	19.9	0.001	2.51E-07	2.51E-01	54.1	0.001	9.24E-08	9.24E-02	19.8	0.001	2.53E-07	2.53E-01
17-6	688.4	6.8	0.001	7.35E-07	7.35E-01	13.2	0.001	3.79E-07	3.79E-01	68.5	0.001	7.30E-08	7.30E-02	31.9	0.001	1.57E-07	1.57E-01
17-7	682.3	10.7	0.001	4.67E-07	4.67E-01	33.2	0.001	1.51E-07	1.51E-01	83.2	0.001	6.01E-08	6.01E-02	26.5	0.001	1.89E-07	1.89E-01
17-8	516.7	6.9	0.001	7.25E-07	7.25E-01	14.8	0.001	3.38E-07	3.38E-01	34.6	0.001	1.45E-07	1.45E-01	26.6	0.001	1.88E-07	1.88E-01
17-9	638.5	3.7	0.001	1.35E-06	1.35E+00	14.9	0.001	3.36E-07	3.36E-01	59.7	0.001	8.38E-08	8.38E-02	10.4	0.001	4.81E-07	4.81E-01
17-10	414.1	3.2	0.001	1.56E-06	1.56E+00	20.9	0.001	2.39E-07	2.39E-01	35.7	0.001	1.40E-07	1.40E-01	18.9	0.001	2.65E-07	2.65E-01
17-11	549.8	6.4	0.001	7.81E-07	7.81E-01	21.5	0.001	2.33E-07	2.33E-01	48.4	0.001	1.03E-07	1.03E-01	35.8	0.001	1.40E-07	1.40E-01
17-12	506.4	5.9	0.001	8.47E-07	8.47E-01	11.5	0.001	4.35E-07	4.35E-01	35.6	0.001	1.40E-07	1.40E-01	52.8	0.001	9.47E-08	9.47E-02
17-13	575.2	7.3	0.001	6.85E-07	6.85E-01	15.5	0.001	3.23E-07	3.23E-01	53.9	0.001	9.28E-08	9.28E-02	23.6	0.001	2.12E-07	2.12E-01
17-14	391.1	9.8	0.001	5.10E-07	5.10E-01	5.5	0.001	9.09E-07	9.09E-01	41.0	0.001	1.22E-07	1.22E-01	27.1	0.001	1.85E-07	1.85E-01
17-15	488.4	5.4	0.001	9.26E-07	9.26E-01	10.0	0.001	5.00E-07	5.00E-01	60.9	0.001	8.21E-08	8.21E-02	33.9	0.001	1.47E-07	1.47E-01
17-16	500.7	5.6	0.001	8.93E-07	8.93E-01	8.5	0.001	5.88E-07	5.88E-01	68.7	0.001	7.28E-08	7.28E-02	15.9	0.001	3.14E-07	3.14E-01
17-17	539.8	7.5	0.001	6.67E-07	6.67E-01	16.6	0.001	3.01E-07	3.01E-01	68.2	0.001	7.33E-08	7.33E-02	45.2	0.001	1.11E-07	1.11E-01
17-18	563.8	8.1	0.001	6.17E-07	6.17E-01	18.0	0.001	2.78E-07	2.78E-01	70.7	0.001	7.07E-08	7.07E-02	41.1	0.001	1.22E-07	1.22E-01
17-19	455.8	6.4	0.001	7.81E-07	7.81E-01	19.8	0.001	2.53E-07	2.53E-01	39.7	0.001	1.26E-07	1.26E-01	17.3	0.001	2.89E-07	2.89E-01
17-20	307.4	3.6	0.001	1.39E-06	1.39E+00	1.5	0.001	3.33E-06	3.33E+00	29.8	0.001	1.68E-07	1.68E-01	21.8	0.001	2.29E-07	2.29E-01
18-1	730.1	9.6	0.001	5.21E-07	5.21E-01	20.9	0.001	2.39E-07	2.39E-01	59.3	0.001	8.43E-08	8.43E-02	26.5	0.001	1.89E-07	1.89E-01
18-2	514.0	6.8	0.001	7.35E-07	7.35E-01	26.5	0.001	1.89E-07	1.89E-01	47.8	0.001	1.05E-07	1.05E-01	20.1	0.001	2.49E-07	2.49E-01
18-3	543.8	4.8	0.001	1.04E-06	1.04E+00	19.8	0.001	2.53E-07	2.53E-01	51.0	0.001	9.80E-08	9.80E-02	42.6	0.001	1.17E-07	1.17E-01
18-4	783.4	8.1	0.001	6.17E-07	6.17E-01	111.4	0.001	4.49E-08	4.49E-02	42.4	0.001	1.18E-07	1.18E-01	32.3	0.001	1.55E-07	1.55E-01
18-5	539.7	2.8	0.001	1.79E-06	1.79E+00	12.7	0.001	3.94E-07	3.94E-01	55.1	0.001	9.07E-08	9.07E-02	38.5	0.001	1.30E-07	1.30E-01
18-6	503.4	2.5	0.001	2.00E-06	2.00E+00	14.7	0.001	3.40E-07	3.40E-01	53.7	0.001	9.31E-08	9.31E-02	27.6	0.001	1.81E-07	1.81E-01
18-7	295.2	0.2	0.001	2.50E-05	2.50E+01	5.8	0.001	8.62E-07	8.62E-01	47.8	0.001	1.05E-07	1.05E-01	16.4	0.001	3.05E-07	3.05E-01
18-8	541.9	6.2	0.001	8.06E-07	8.06E-01	17.4	0.001	2.87E-07	2.87E-01	38.5	0.001	1.30E-07	1.30E-01	17.7	0.001	2.82E-07	2.82E-01
18-9	499.8	5.6	0.001	8.93E-07	8.93E-01	23.2	0.001	2.16E-07	2.16E-01	46.4	0.001	1.08E-07	1.08E-01	22.7	0.001	2.20E-07	2.20E-01
18-10	511.2	3.6	0.001	1.39E-06	1.39E+00	17.5	0.001	2.86E-07	2.86E-01	56.3	0.001	8.88E-08	8.88E-02	31.9	0.001	1.57E-07	1.57E-01
18-11	406.5	5.0	0.001	1.00E-06	1.00E+00	8.2	0.001	6.10E-07	6.10E-01	43.7	0.001	1.14E-07	1.14E-01	10.4	0.001	4.81E-07	4.81E-01
18-12	504.0	4.5	0.001	1.11E-06	1.11E+00	5.2	0.001	9.62E-07	9.62E-01	69.6	0.001	7.18E-08	7.18E-02	24.6	0.001	2.03E-07	2.03E-01
18-13	542.6	4.6	0.001	1.09E-06	1.09E+00	16.3	0.001	3.07E-07	3.07E-01	73.3	0.001	6.82E-08	6.82E-02	36.6	0.001	1.37E-07	1.37E-01
18-14	658.0	6.6	0.001	7.58E-07	7.58E-01	16.7	0.001	2.99E-07	2.99E-01	62.8	0.001	7.96E-08	7.96E-02	43.5	0.001	1.15E-07	1.15E-01
18-15	508.0	5.9	0.001	8.47E-07	8.47E-01	8.2	0.001	6.10E-07	6.10E-01	38.5	0.001	1.30E-07	1.30E-01	21.2	0.001	2.36E-07	2.36E-01
18-16	585.2	7.1	0.001	7.04E-07	7.04E-01	15.2	0.001	3.29E-07	3.29E-01	63.1	0.001	7.92E-08	7.92E-02	49.1	0.001	1.02E-07	1.02E-01
18-17	612.4	6.9	0.001	7.25E-07	7.25E-01	15.8	0.001	3.16E-07	3.16E-01	61.8	0.001	8.09E-08	8.09E-02	40.0	0.001	1.25E-07	1.25E-01
18-18	557.2	4.8	0.001	1.04E-06	1.04E+00	8.9	0.001	5.62E-07	5.62E-01	65.1	0.001	7.68E-08	7.68E-02	21.0	0.001	2.38E-07	2.38E-01
18-19	409.2	2.8	0.001	1.79E-06	1.79E+00	3.7	0.001	1.35E-06	1.35E+00	43.9	0.001	1.14E-07	1.14E-01	37.4	0.001	1.34E-07	1.34E-01
18-20	517.2	2.3	0.001	2.17E-06	2.17E+00	5.2	0.001	9.62E-07	9.62E-01	31.4	0.001	1.59E-07	1.59E-01	18.7	0.001	2.67E-07	2.67E-01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
all - avg	564.7	3.8	0.007	1.04E-05	1.04E+01	12.4	0.060	0.000	2.30E+01	45.1	0.035	0.000	3.66E+00	18.4	0.066	1.58E-05	1.58E+01
all-count	361.0	359.0	360.000	3.59E+02	3.59E+02	361.0	361.000	361.000	3.61E+02	361.0	361.000	361.000	3.61E+02	359.0	361.000	359.000	3.59E+02
all-std	100.364	2.131	0.008	1.04E-05	1.04E+01	8.729	0.183	0.000	5.59E+01	18.464	0.050	0.000	4.79E+00	11.372	0.140	0.000	2.97E+01
male avg	570.7	3.6	0.0	8.92E-06	8.92E+00	10.9	0.1	0.0	2.40E+01	42.8	0.0	0.0	2.73E+00	15.3	0.056	0.000	1.39E+01
male count	181.0	180.0	181.0	1.80E+02	1.80E+02	181.0	181.0	181.0	1.81E+02	181.0	181.0	181.0	1.81E+02	179.0	181.000	179.000	1.79E+02
male std	103.014	2.188	0.009	9.27E-06	9.27E+00	7.900	0.210	0.000	6.62E+01	18.362	0.044	0.000	3.41E+00	10.820	0.123	0.000	2.62E+01
female avg	558.6	4.0	0.0	1.18E-05	1.18E+01	13.9	0.1	0.0	2.20E+01	47.4	0.0	0.0	4.60E+00	21.5	0.076	0.000	1.76E+01
fem cnt	180.0	179.0	179.0	1.79E+02	1.79E+02	180.0	180.0	180.0	1.80E+02	180.0	180.0	180.0	1.80E+02	180.0	180.000	180.000	1.80E+02
fem std	97.596	2.138	0.008	1.19E-05	1.19E+01	10.199	0.149	0.000	4.14E+01	13.404	0.051	0.000	5.50E+00	11.932	0.152	0.000	3.17E+01
Tank 1 high male																	
avg	556.9	4.2	0.017	1.72E-05	1.72E+01	14.3	0.246	0.000	7.64E+01	59.733	0.084	0.000	6.66E+00	26.1	0.227	0.000	4.48E+01
count	21.0	20.0	21.000	2.00E+01	2.00E+01	21.0	21.000	21.000	2.10E+01	21.0	21.000	21.000	2.10E+01	21.0	21.0	21.0	2.10E+01
std	88.498	1.510	0.020	1.29E-05	1.29E+01	10.309	0.563	0.000	1.45E+02	14.786	0.068	0.000	4.36E+00	10.082	0.223	0.000	4.03E+01
Tank 2 high male																	
avg	575.0	3.3	0.008	1.63E-05	1.63E+01	7.0	0.063	0.000	6.20E+01	36.4	0.039	0.000	5.31E+00	10.4	0.041	0.000	1.79E+01
count	20	20	20.000	2.00E+01	2.00E+01	20	20.000	20.000	2.00E+01	20	20.000	20.000	2.00E+01	20	20	20	2.00E+01
std	73.299	1.707	0.003	1.15E-05	1.15E+01	2.790	0.059	0.000	1.06E+02	15.969	0.026	0.000	2.95E+00	4.398	0.035	0.000	1.15E+01
Tank 3 high male																	
avg	617.5	4.9	0.013	1.43E-05	1.43E+01	16.6	0.163	0.000	4.98E+01	57.1	0.092	0.000	8.01E+00	22.6	0.193	0.000	4.75E+01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	19.0	20.0	19.0	1.90E+01
std	101.153	1.917	0.005	3.74E-06	3.74E+00	8.557	0.152	0.000	3.79E+01	18.554	0.064	0.000	4.91E+00	8.582	0.175	0.000	4.74E+01
Tank 1,2,3 high male																	
avg	582.7	4.1	0.013	1.59E-05	1.59E+01	12.7	0.159	0.000	6.30E+01	51.2	0.072	0.000	6.66E+00	19.7	0.155	0.000	3.67E+01
count	61.0	60.0	61.000	6.00E+01	6.00E+01	61.0	61.000	61.000	6.10E+01	61.0	61.000	61.000	6.10E+01	60.0	61.0	60.0	6.00E+01
std	90.603	1.814	0.012	1.01E-05	1.01E+01	8.839	0.346	0.000	1.06E+02	19.303	0.060	0.000	4.23E+00	10.483	0.183	0.000	3.82E+01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001 detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
Tank 4 high fem																	
avg	578.9	3.0	0.010	2.15E-05	2.15E+01	10.0	0.075	0.000	4.14E+01	38.8	0.072	0.000	9.12E+00	10.3	0.070	0.000	3.06E+01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	100.427	1.797	0.002	1.17E-05	1.17E+01	4.544	0.055	0.000	4.56E+01	10.974	0.039	0.000	4.27E+00	5.945	0.084	0.000	2.80E+01
Tank 5 high fem																	
avg	521.1	4.1	0.018	2.26E-05	2.26E+01	13.7	0.229	0.000	6.74E+01	50.0	0.127	0.000	1.30E+01	26.9	0.360	0.000	6.97E+01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	88.561	1.713	0.009	7.47E-06	7.47E+00	6.778	0.353	0.000	6.93E+01	9.462	0.078	0.000	7.79E+00	10.942	0.306	0.000	6.22E+01
Tank 6 high fem																	
avg	585.9	3.2	0.011	2.17E-05	2.17E+01	11.0	0.123	0.000	5.24E+01	40.2	0.075	0.000	9.20E+00	13.2	0.086	0.000	2.72E+01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	69.570	1.484	0.003	1.19E-05	1.19E+01	5.243	0.167	0.000	6.12E+01	11.796	0.038	0.000	3.89E+00	6.086	0.095	0.000	2.19E+01
Tank 4,5,6 high fem																	
avg	561.9	3.4	0.013	2.19E-05	2.19E+01	11.6	0.142	0.000	5.37E+01	43.0	0.091	0.000	1.04E+01	16.8	0.172	0.000	4.25E+01
count	60.0	60.0	60.000	6.00E+01	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01
std	90.503	1.714	0.007	1.04E-05	1.04E+01	5.720	0.233	0.000	5.95E+01	11.722	0.060	0.000	5.79E+00	10.718	0.231	0.000	4.51E+01
Tank 7 low male																	
avg	546.0	5.3	0.007	7.97E-06	7.97E+00	12.9	0.027	0.000	1.00E+01	60.3	0.011	0.000	9.60E-01	19.1	0.014	0.000	3.68E+00
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	75.951	3.188	0.002	3.34E-06	3.34E+00	5.360	0.031	0.000	9.42E+00	11.385	0.002	0.000	1.60E-01	6.694	0.006	0.000	9.67E-01
Tank 8 low male																	
avg	555.7	2.4	0.004	7.76E-06	7.76E+00	7.0	0.007	0.000	6.12E+00	33.2	0.008	0.000	1.39E+00	8.3	0.008	0.000	4.75E+00
count	20	20	20.000	2.00E+01	2.00E+01	20	20.000	20.000	2.00E+01	20	20.000	20.000	2.00E+01	20	20.000	20.000	2.00E+01
std	161.781	1.458	0.003	4.65E-06	4.65E+00	3.989	0.003	0.000	2.64E+00	12.015	0.001	0.000	6.34E-01	3.135	0.003	0.000	1.86E+00
Tank 9 low male																	
avg	537.2	3.7	0.005	8.05E-06	8.05E+00	11.6	0.010	0.000	4.50E+00	51.4	0.009	0.000	1.15E+00	15.8	0.011	0.000	3.71E+00
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	79.546	1.807	0.002	5.86E-06	5.86E+00	4.169	0.007	0.000	2.65E+00	26.762	0.002	0.000	8.00E-01	7.295	0.006	0.000	2.40E+00

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
Tank 7,8,9 low male																	
avg	546.0	5.3	0.007	7.97E-06	7.97E+00	12.9	0.027	0.000	1.00E+01	60.3	0.011	0.000	9.60E-01	19.1	0.014	0.000	3.68E+00
count	60.0	60.0	60.000	6.00E+01	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01
std	111.274	2.531	0.003	4.65E-06	4.65E+00	5.152	0.020	0.000	6.21E+00	21.168	0.002	0.000	6.12E-01	7.460	0.005	0.000	1.88E+00
Tank 10 low fem																	
avg	550.5	3.9	0.010	1.42E-05	1.42E+01	18.3	0.063	0.000	1.59E+01	53.0	0.045	0.000	4.28E+00	28.4	0.077	0.000	1.35E+01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	94.492	1.691	0.002	4.66E-06	4.66E+00	11.361	0.070	0.000	1.16E+01	12.558	0.015	0.000	9.72E-01	7.601	0.036	0.000	6.23E+00
Tank 11 low fem																	
avg	584.0	5.1	0.010	1.08E-05	1.08E+01	17.2	0.036	0.000	1.09E+01	53.9	0.025	0.000	2.23E+00	31.9	0.060	0.000	9.37E+00
count	20.0	19.0	19.000	1.90E+01	1.90E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	108.826	2.645	0.013	1.70E-05	1.70E+01	7.040	0.031	0.000	7.96E+00	14.971	0.010	0.000	4.11E-01	11.250	0.028	0.000	3.47E+00
Tank 12 low fem																	
avg	616.2	2.7	0.004	1.03E-05	1.03E+01	12.4	0.021	0.000	8.18E+00	46.5	0.031	0.000	3.25E+00	13.6	0.024	0.000	7.51E+00
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	104.052	1.422	0.001	4.61E-06	4.61E+00	4.080	0.014	0.000	3.51E+00	12.450	0.011	0.000	5.90E-01	7.001	0.026	0.000	3.42E+00
Tk 10,11,12 low fem																	
avg	583.6	3.9	0.008	1.18E-05	1.18E+01	16.0	0.040	0.000	1.17E+01	51.1	0.034	0.000	3.25E+00	24.6	0.054	0.000	1.01E+01
count	60.0	59.0	59.000	5.90E+01	5.90E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01
std	104.434	2.187	0.008	1.04E-05	1.04E+01	8.333	0.047	0.000	8.84E+00	13.570	0.015	0.000	1.09E+00	11.785	0.037	0.000	5.15E+00
Tank 13 ctl male																	
avg	619.7	2.9	0.001	2.72E-06	2.72E+00	9.3	0.001	0.000	6.46E-01	24.2	0.001	0.000	3.46E-01	10.7	0.001	0.000	6.27E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	73.875	1.492	0.000	2.61E-06	2.61E+00	4.495	0.000	0.000	2.77E-01	7.791	0.002	0.000	5.55E-01	5.614	0.000	0.000	4.16E-01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001 detection limit for calculation purposes)

Fish ID	Fish Wt. mg	Blood Wt mg	Blood Chem mg/L	Blood mg/mg	Blood mg/L	Liver Wt mg	Liv. chem mg/L	Liver mg/mg	Liver mg/L	Mus. Wt mg	Muscle chem	Muscle mg/mg	Muscle mg/L	Gill Wt mg	Gill Chem mg/L	Gill mg/mg	Gill mg/L
Tank 14																	
ctl male																	
avg	589.4	2.9	0.001	3.30E-06	3.30E+00	12.4	0.001	0.000	5.36E-01	38.0	0.001	0.000	2.13E-01	13.7	0.001	0.000	4.83E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	115.107	1.703	0.001	4.14E-06	4.14E+00	4.625	0.001	0.000	3.27E-01	24.318	0.000	0.000	1.58E-01	7.595	0.000	0.000	2.67E-01
Tank 15																	
ctl male																	
avg	539.5	2.7	0.001	2.66E-06	2.66E+00	6.7	0.001	0.000	3.36E+00	23.7	0.001	0.000	3.35E-01	10.5	0.001	0.000	1.12E+00
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	19.0	20.000	19.000	1.90E+01
std	105.275	1.904	0.000	1.69E-06	1.69E+00	3.866	0.000	0.000	1.10E+01	18.565	0.000	0.000	3.07E-01	14.325	0.000	0.000	8.78E-01
Tk13,14,15																	
ctl male																	
avg	582.9	2.8	0.001	2.90E-06	2.90E+00	9.5	0.001	0.000	1.51E+00	28.6	0.001	0.000	2.98E-01	11.6	0.001	0.000	7.38E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	19.0	20.000	19.000	1.90E+01
std	103.467	1.681	0.001	2.95E-06	2.95E+00	4.883	0.001	0.000	6.38E+00	19.119	0.001	0.000	3.76E-01	9.751	0.000	0.000	6.28E-01
Tank 16																	
ctl fem																	
avg	516.1	3.0	0.001	2.14E-06	2.14E+00	8.4	0.001	0.000	8.68E-01	37.6	0.001	0.000	1.41E-01	12.5	0.001	0.000	4.76E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	63.774	1.357	0.000	1.33E-06	1.33E+00	2.871	0.000	0.000	1.12E+00	8.083	0.000	0.000	3.82E-02	5.688	0.000	0.000	1.90E-01
Tank 17																	
ctl fem																	
avg	536.5	6.1	0.001	9.23E-07	9.23E-01	15.5	0.001	0.000	5.11E-01	54.3	0.001	0.000	9.96E-02	28.1	0.001	0.000	2.07E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	99.925	2.072	0.000	3.63E-07	3.63E-01	6.876	0.000	0.000	6.86E-01	14.688	0.000	0.000	3.02E-02	10.812	0.000	0.000	9.12E-02
Tank 18																	
ctl fem																	
avg	538.1	5.0	0.001	2.30E-06	2.30E+00	18.7	0.001	0.000	4.71E-01	52.6	0.001	0.000	9.97E-02	28.9	0.001	0.000	2.01E-01
count	20.0	20.0	20.000	2.00E+01	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01	20.0	20.000	20.000	2.00E+01
std	107.361	2.246	0.000	5.36E-06	5.36E+00	22.755	0.000	0.000	3.31E-01	11.313	0.000	0.000	2.31E-02	10.682	0.000	0.000	9.00E-02
Tk17,18,19																	
ctl fem																	
avg	530.3	4.7	0.001	1.79E-06	1.79E+00	14.2	0.001	0.000	6.17E-01	48.1	0.001	0.000	1.13E-01	23.2	0.001	0.000	2.95E-01
count	60.0	60.0	60.000	6.00E+01	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01	60.0	60.000	60.000	6.00E+01
std	91.319	2.294	0.000	3.20E-06	3.20E+00	14.263	0.000	0.000	7.91E-01	13.751	0.000	0.000	3.63E-02	11.958	0.000	0.000	1.83E-01

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Group ID	Kidney wt mg	Kid.chem. mg/L	Kidney mg/mg	Kidney mg/L	Spleen wt mg	Spl. Chem	Spleeen mg/mg	Spleen mg/L
	avg of grp kidney				avg of grp spleen			
1	4.700	no data			1.750	1.718	4.91E-03	4.91E+03
2	2.000	0.033	8.25E-05	8.25E+01	0.400	0.074	9.25E-04	9.25E+02
3	4.000	0.160	2.00E-04	2.00E+02	0.200	1.772	4.43E-02	4.43E+04
4	1.200	0.023	9.58E-05	9.58E+01	0.500	0.077	7.70E-04	7.70E+02
5	0.900	0.007	3.89E-05	3.89E+01	2.800	1.331	2.38E-03	2.38E+03
6	1.400	0.032	1.14E-04	1.14E+02	0.400	0.015	1.88E-04	1.88E+02
7	3.200	0.014	2.19E-05	2.19E+01	0.900	0.130	7.22E-04	7.22E+02
8	2.400	0.008	1.67E-05	1.67E+01	0.500	0.014	1.40E-04	1.40E+02
9	1.700	0.007	2.06E-05	2.06E+01	0.600	0.024	2.00E-04	2.00E+02
10	2.300	0.040	8.70E-05	8.70E+01	2.200	0.236	5.36E-04	5.36E+02
11	2.300	0.025	5.43E-05	5.43E+01	1.900	0.106	2.79E-04	2.79E+02
12	3.000	0.014	2.33E-05	2.33E+01	0.900	0.047	2.61E-04	2.61E+02
13	1.940	0.001	2.58E-06	2.58E+00	0.500	0.001	1.00E-05	1.00E+01
14	2.300	0.001	2.17E-06	2.17E+00	1.100	0.001	4.55E-06	4.55E+00
15	1.300	0.001	3.85E-06	3.85E+00	0.400	0.001	1.25E-05	1.25E+01
16	1.000	0.001	5.00E-06	5.00E+00	0.600	0.001	8.33E-06	8.33E+00
17	1.400	0.001	3.57E-06	3.57E+00	1.800	0.001	2.78E-06	2.78E+00
18	2.300	0.001	2.17E-06	2.17E+00	2.400	0.001	2.08E-06	2.08E+00

Appendix I. BDCM Tissue Levels in Medaka (shaded areas were below detection limits and changed to the 0.001detection limit for calculation purposes)

Group ID	Kidney wt mg	Kid.chem. mg/L	Kidney mg/mg	Kidney mg/L	Spleen wt mg	Spl. Chem	Spleeen mg/mg	Spleen mg/L
all - avg	2.186	0.022	0.000	4.56E+01	1.103	0.308	0.003	3.09E+03
all-count	18.000	17.000	17.000	1.70E+01	18.000	18.000	18.000	1.80E+01
all-std	1.023	0.038	0.000	5.45E+01	0.815	0.606	0.010	1.04E+04

Appendix II: Model code

```
Program: medpdl in Medaka
!Jason L Boyd and J W Fisher, PhD
!13 Nov 2001
!metabolism - MM in liver, based on rat values (Nichols etal, 1998)
!(Km('scaling' Km effectively decrease affinity), scaled Vmax)
!partitions - using "concentration ratios" from low dose medaka males
!blood flow - gill compartment sans segmental (parallel) gill blood flow, only serial blood flow
!gill volume QGC=1.0
!subtracting fractional gill volume (0.1) from !the muscle tissue compartment which Nichols etal 1993 call
!'viscera'
!GEE is set to 0.07
!QPC 7.2, Nichols etal, 1996
![Nichols etal, 1996 compares channel cats & rainbow trout PBTK]
!--not presented here, may provide better description of flux at gill
!--see McKim etal 1985
!--------------------------initial section for constants-------------------
INITIAL

CONSTANT QPC=7.06          !rate of uptake at the gill (L/(kgh))(Nichols etal1993, Qw)
CONSTANT QCC=2.07          !cardiac output (L/(kgh))(Nichols etal 1991, 1993)
CONSTANT QLC=0.03          !fraction blood flow to liver (Nichols etal 1991,1993)
CONSTANT QMC=0.6           !fraction blood flow to muscle (Nichols etal 1991,1993)
CONSTANT QGC=1.0           !fraction blood flow to gills
CONSTANT PGW=24            !partition gill/water
CONSTANT PB=4.62           !partition gill/blood
CONSTANT PL=1.3            !partition liver/blood
CONSTANT PM=0.12           !partition muscle/blood
CONSTANT PO=18             !partition other/blood (from rat fat)
CONSTANT BW=0.0005         !bw of individual fish (kg)
CONSTANT VLC=0.015         !fractional volume of liver tissue (Nichols etal 1991/3)
CONSTANT VMC=0.781         !fractional volume of muscle tissue (Nichols etal 1991/3)
CONSTANT VOC=0.094         !fractional volume of 'other' tissue (subtraction)
CONSTANT VGC=0.10          !fractional volume of gill tissue (estimation)
CONSTANT VMAXC=12.8        !max rate of hepatic metabolism (mg/hkg)
CONSTANT KMC=0.5           !Michelis-Menten rate constant (mg/L)
CONSTANT KFC=0.000000000001  !1st order rate constant (h-1)
CONSTANT CONC=1.5          !conc in water (mg/L)
CONSTANT GEE=0.07          !gill extraction efficiency water to gill

'Timing commands'

CONSTANT CINT=0.05
CONSTANT TSTOP=8.5
CONSTANT TCHNG=4           !time (h) of exposure

'SCALED PARAMETERS'
QC=QCC*BW**0.75     !(L/h) bwscaled cardiac output
QP=QPC*BW**0.75     !(L/h) bwscaled rate of uptake at gill
QL=QLC*QC
QM=QMC*QC
QG=QGC*QC
QO=QC-QL-QM         !QO the rate of bl flow left over to go to 'other' tissues
VL=VLC*BW
```

```
VM=VMC*BW
VO=VOC*BW
VG=VGC*BW
KF=KFC*BW**0.75       !Nichols etal1993 assumed no biotransf
VMAX=VMAXC*BW**0.75   !Nichols etal, 1998
KM=KMC          !Nichols etal, 1998

END                  !'END OF INITIAL'
!---------------------DYNAMIC SECTION---------------------------------------

DYNAMIC
ALGORITHM IALG=2          !2 IS GEAR'S STIFF
!-----------------DERIVATIVE SECTION----------------------------------------
DERIVATIVE
!-----------------'INHALATION' SECTION--------------------------------------

procedural
pflag = pulse(0.,20.,tchng)            !Inhalation switch for on or off
CI   = CONC*pflag         !Inhaled conc
end

!--------------------model code----------------------------------------------

'AG  =  amount in gill (mg)'
RAG  =  QC*(CT - CA) + QP*(CI*PGW*GEE - CX)
!RAG  =  QC*(CT - CA) + QP*((CI - CX)/((RM/PGW) - RAQ)
!SEE YALKOWSKI & MOROZOWICH 1980 AND
!MCKIM ETAL 1985
AG  =  INTEG(RAG,0.)
CA  =  AG/(VG*PB)
CG  =  AG/VG
AUCG =  INTEG(CG,0.)
AUCA =  INTEG(CA,0.)
RAI  =  QP*CI*PGW            !this is rate of amount input into gill from water
AI  =  INTEG(RAI,0.)
CX  =  GEE*CG/PGW
RAX  =  QP*CX
AX  =  INTEG(RAX,0.)
DOSEINH =  AI-AX             !a measure of extraction efficiency

'AM  =  amount in muscle (mg)'
RAM  =  QM*(CA-CVM)
AM  =  INTEG(RAM,0.)
CVM  =  AM/(VM*PM)
CM  =  AM/VM
AUCM =  INTEG(CM,0.)

'AL  =  amount in liver (mg)'
RAL  =  QL*(CA-CVL)-RAMX
AL1  =  INTEG(RAL,0.)
AL  =  MAX(AL1,0.)
CVL  =  AL/(VL*PL)
CL  =  AL/VL
AUCL =  INTEG(CL,0.)
AUCLW = AUCL/168
AUCLM = AUCL/720
```

Appendix II: Model code

```
!the AL and AL1 statement is an attempt to fix the concentration from going below zero

'AMX = amount metabolized (mg)'
RAMX = VMAX*CL/(KM+CL)
AMX = INTEG(RAMX,0.)
AMXW = AMX/168
AMXM = AMX/720
CMX = AMX/VL
AUCX = INTEG(CMX,0.)
AUCXW = AUCX/168
AUCLM = AUCX/720

'AO = amount in other tissue compartment (mg)'
RAO = QO*(CA-CVO)
AO = INTEG(RAO,0.)
CVO = AO/(VO*PO)
CO = AO/VO
AUCO = INTEG(CO,0.)

'CV = mixed venous blood concentration (mg/L)'
CV = (QM*CVM + QL*CVL + QO*CVO)/QC
CVAUC= INTEG(CV,0.)

'CT = concentration (mg/L) while in transit arterially from heart to gill'
CT = CV

'TMASS = mass balance (mg)'
TMASS = AL+AM+AO+AX+AMX

'DOSEX = net amount absorbed (mg)'
DOSEX = AI-AX-AMX            !I added AMX to this because AMX would be leaving also

TERMT(T.GE.TSTOP)


END     !'end of derivative'
END     !'end of dynamic'
END     !'end of program'


! File: med.cmd
! medaka pbpk cmd
! Jason L. Boyd and Jeff Fisher, PhD
! procedures: 3 sets of different partitions, automatically run and plot

procedure parthm
s pgw=2.45, pb=2.31, pl=3.96, pm=0.42
s title(1)='BDCM in CV, CL, high conc ratios'
end

!do not put a semicolon in title, semicolon truncates title
procedure partlm
s title(1)='BDCM in CV, CL, low conc ratios'
s pgw=2.45, pb=0.46, pl=1.25, pm=0.12
end
```

Appendix II: Model code

```
!first line mean, 2nd line -sd, 3rd line +sd
DATA mhi &
(t, cv, cl, cm, cg)
4.01, 15.9, 63.0, 6.66, 36.7
4.01, 5.8, 0.0001, 2.43, 0.0001
4.01, 26.0, 169, 10.9, 74.9
end

!first line mean, 2nd line -sd, 3rd line +sd
DATA mlo &
(t, cv, cl, cm, cg)
4.01, 7.97, 10.0, 0.96, 3.68
4.01, 3.32, 3.79, 0.348, 1.8
4.01, 12.6, 16.2, 1.57, 5.56
end

!following data excluded in preference to total averaged lump data
!data for males high dose
!DATA mhigh &
!(t, cv, cl, cm, cg)
!4.017, 0.67, 2.54, 0.53, 2.7
!4.25, 0.60, 1.82, 0.28, 1.42
!5.0, 0.535, 1.46, 0.19, 0.99
!end
!
!data for males low dose
!DATA mlow &
!(t, cv, cl, cm, cg)
!4.017, 0.31, 0.22, 0.06, 0.18
!4.25, 0.29, 0.23, 0.06, 0.18
!5.0, 0.29, 0.23, 0.04, 0.14
!end
!
!data for females high dose
!DATA fhigh &
!(t, cv, cl, cm, cg)
!4.017, 1.07, 3.67, 0.92, 4.99
!4.25, 0.77, 2.80, 0.49, 1.87
!5.0, 0.832, 1.13, 0.30, 0.92
!end
!
!data for females low dose
!DATA flow &
!(t, cv, cl, cm, cg)
!4.017, 0.43, 0.69, 0.14, 0.41
!4.25, 0.42, 0.44, 0.14, 0.44
!5.0, 0.41, 0.42, 0.12, 0.35
!end
!previous 'data' block excluded in favor of analyzing data as end of exposure, lumped data

s weditg=.false.  !suppress output from schedule
s hvdprn=.false.  !suppress high volume display

prepare t,cv,cl,cm,cg,co,cvauc,aucl,dosex

procedure plth
```

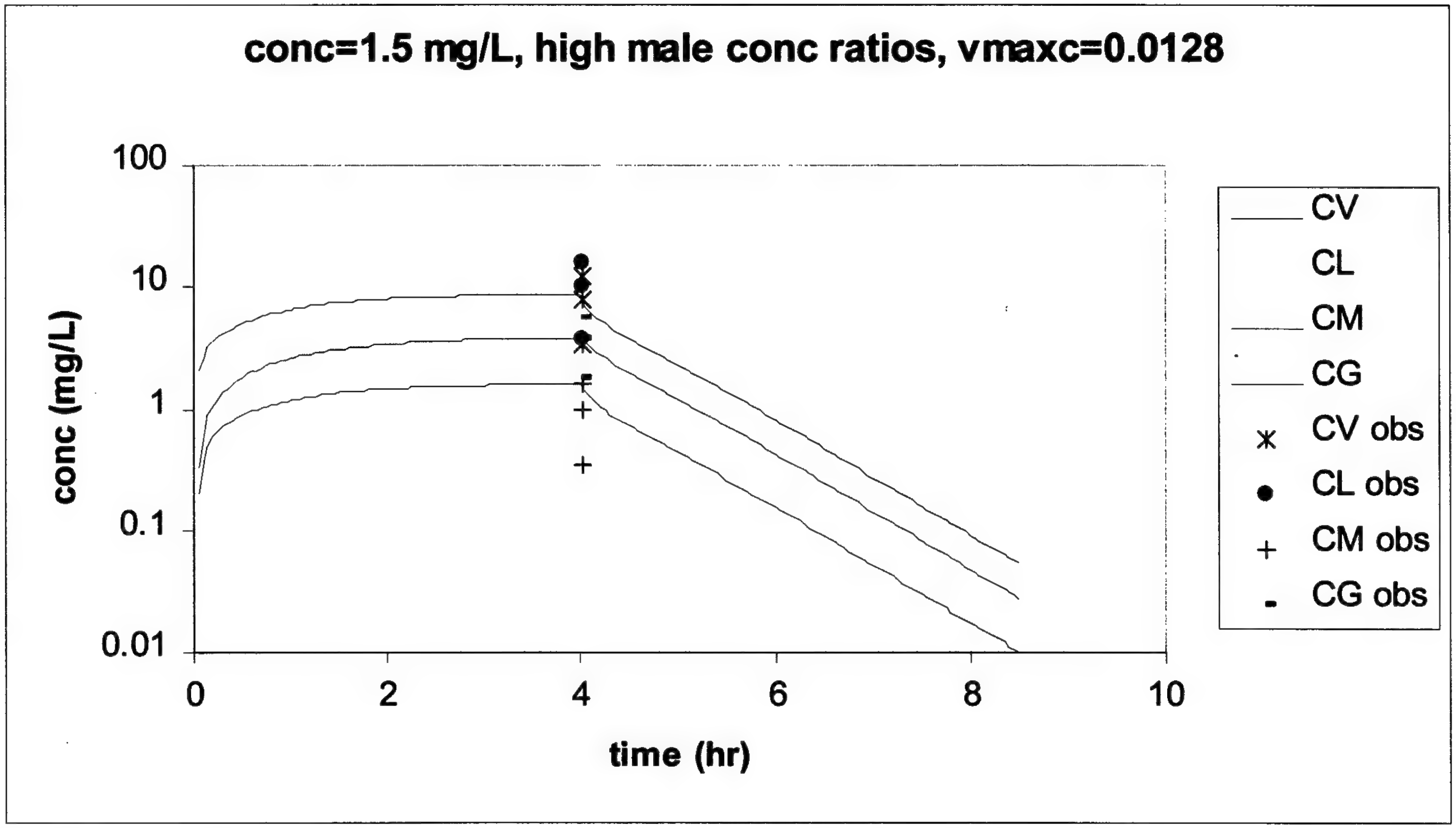
Appendix II: Model code

```
start
plot /data=mhi cv /lo=-100 /hi=200 /tag='(mg/L)' /char=2, cl /char=3, cm /char=4, cg /char=5 /same
end

procedure pltl
start
plot /data=mlo cv /lo=-10 /hi=50 /tag='(mg/L)' /char=2, cl /char=3, cm /char=4, cg /char=5 /same
end

procedure hirun
s conc=15, title(37)='conc=15.0 mg/L'
parthm
s vmaxc=0, title(52)='vmaxc=0.0000'
plth
s vmaxc=0.128, title(52)='vmaxc=0.0128'
plth
s vmaxc=0.128, title(52)='vmaxc=0.1280'
plth
s vmaxc=1.28, title(52)='vmaxc=1.2800'
plth
partlm
s vmaxc=0, title(52)='vmaxc=0.0000'
plth
s vmaxc=0.128, title(52)='vmaxc=0.0128'
plth
s vmaxc=0.128, title(52)='vmaxc=0.1280'
plth
s vmaxc=1.28, title(52)='vmaxc=1.2800'
plth
end

procedure lorun
s conc=1.5, title(37)='conc=1.50 mg/L'
parthm
s vmaxc=0, title(52)='vmaxc=0.000'
pltl
s vmaxc=0.128, title(52)='vmaxc=0.128'
pltl
s vmaxc=1.28, title(52)='vmaxc=1.280'
pltl
s vmaxc=12.8, title(52)='vmaxc=12.80'
pltl
partlm
s vmaxc=0, title(52)='vmaxc=0.000'
pltl
s vmaxc=0.128, title(52)='vmaxc=0.128'
pltl
s vmaxc=1.28, title(52)='vmaxc=1.280'
pltl
s vmaxc=12.8, title(52)='vmaxc=12.80'
pltl
end

procedure po18
s po=18, title(65)='po=18'
hirun
```

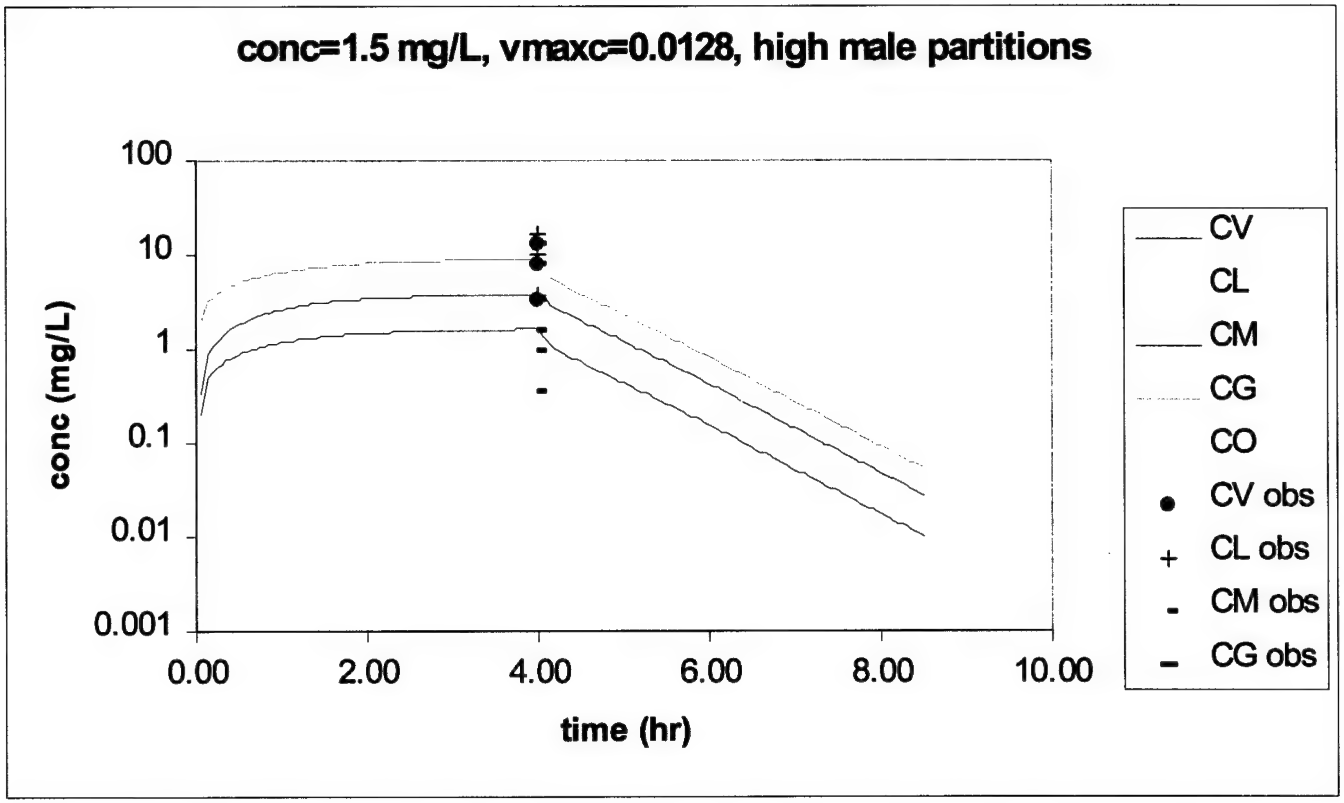
```
lorun
end

procedure po25
s po=25, title(65)='po=25'
hirun
lorun
end

procedure po28
s po=28, title(65)='po=28'
hirun
lorun
end

procedure po30
s po=30, title(65)='po=30'
hirun
lorun
end

procedure po23
s po=23, title(65)='po=23'
hirun
lorun
end

procedure po21
s po=21, title(65)='po=21'
hirun
lorun
end

procedure run2
s conc=15, title(37)='conc=15.0 mg/L'
s vmaxc=0, title(52)='vmaxc=0.0000'
plth
s conc=1.5, title(37)='conc'1.50 mg/L'
s vmaxc=0, title(52)='vmaxc=0.0000'
pltl
s conc=15, title(37)='conc=15.0 mg/L'
s vmaxc=0.0128, title(52)='vmaxc=0.0128'
plth
s conc=1.5, title(37)='conc=1.50 mg/L'
s vmaxc=0.0128, title(52)='vmaxc=0.0128'
pltl
s conc=15, title(37)='conc=15.0 mg/L'
s vmaxc=0.128, title(52)='vmaxc=0.1280'
plth
s conc=1.5, title(37)='conc'1.50 mg/L'
s vmaxc=0.128, title(52)='vmaxc=0.1280'
pltl
s conc=15, title(37)='conc=15.0 mg/L'
s vmaxc=1.28, title(52)='vmaxc=1.2800'
plth
s conc=1.5, title(37)='conc'1.50 mg/L'
```

```
s vmaxc=1.28, title(52)='vmaxc=1.2800'
pltl
s conc=15, title(37)='conc=15.0 mg/L'
s vmaxc=12.8, title(52)='vmaxc=12.800'
plth
s conc=1.5, title(37)='conc'1.50 mg/L'
s vmaxc=12.8, title(52)='vmaxc=12.800'
pltl
end

procedure bycoef
parthm
run2
partlm
run2
end

procedure bypo
s po=18, title(65)='po=18'
bycoef.
s po=21, title(65)='po=21'
bycoef
s po=25, title(65)='po=25'
bycoef
s po=28, title(65)='po=28'
bycoef
end

procedure doit
po18
po30
end
```

Appendix III. PBPK Plot Simulations

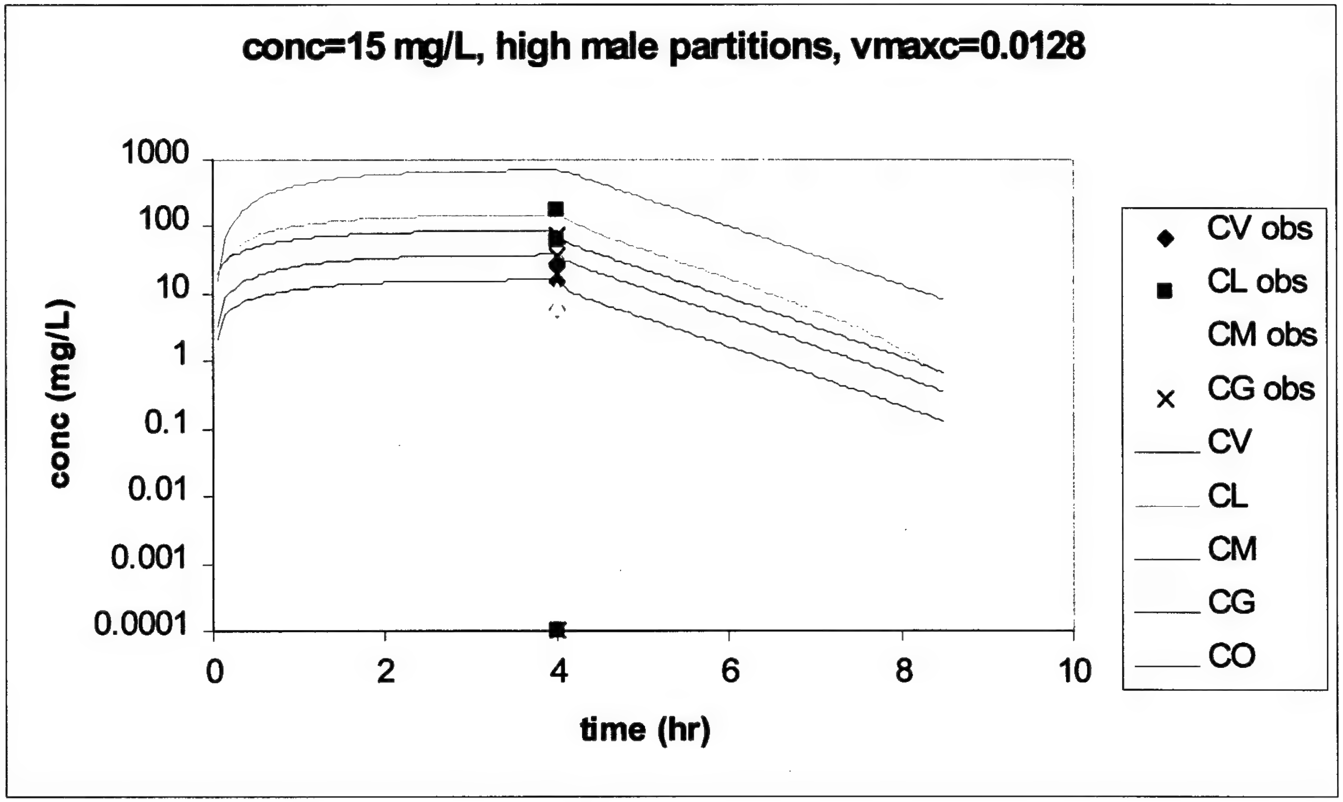


Plot I: Simulation at low concentration using high dosed male concentration ratios as partitions, with Vmaxc=0.0128 Above simulation includes simulated concentrations in four tissues, venous blood, liver, muscle, and gill, represented as smooth lines. The sharp drop in liver concentrations after six hours is due to the fact that metabolism is "turned on" in the ACSL code and the ACSL is having trouble integrating close to zero. Observed concentrations and + and - one standard deviation are represented by the points at the four hour mark.

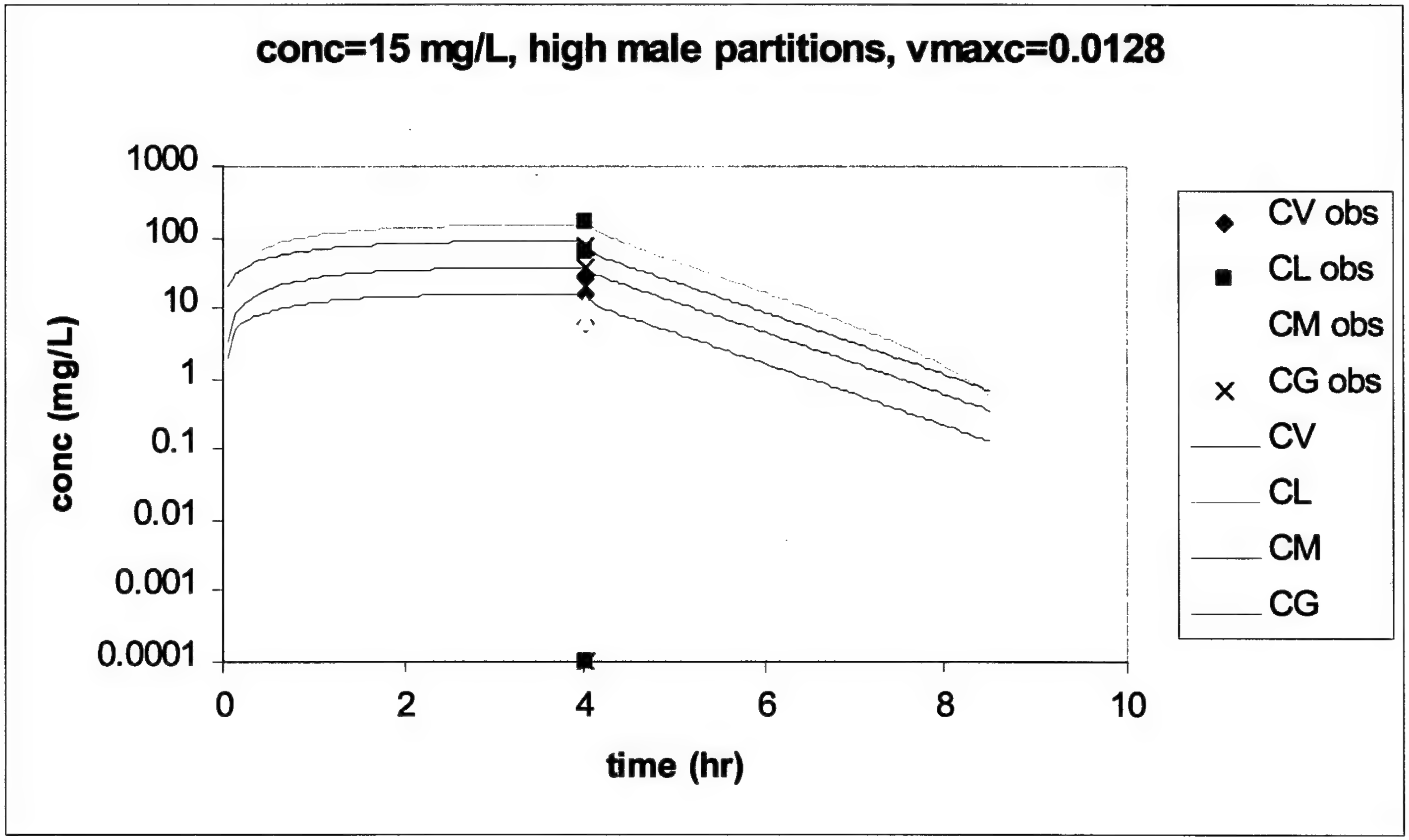


Plot II: Simulation at low concentration using high dosed male concentration ratios as partitions (same as plot I, except includes the "other" compartment)

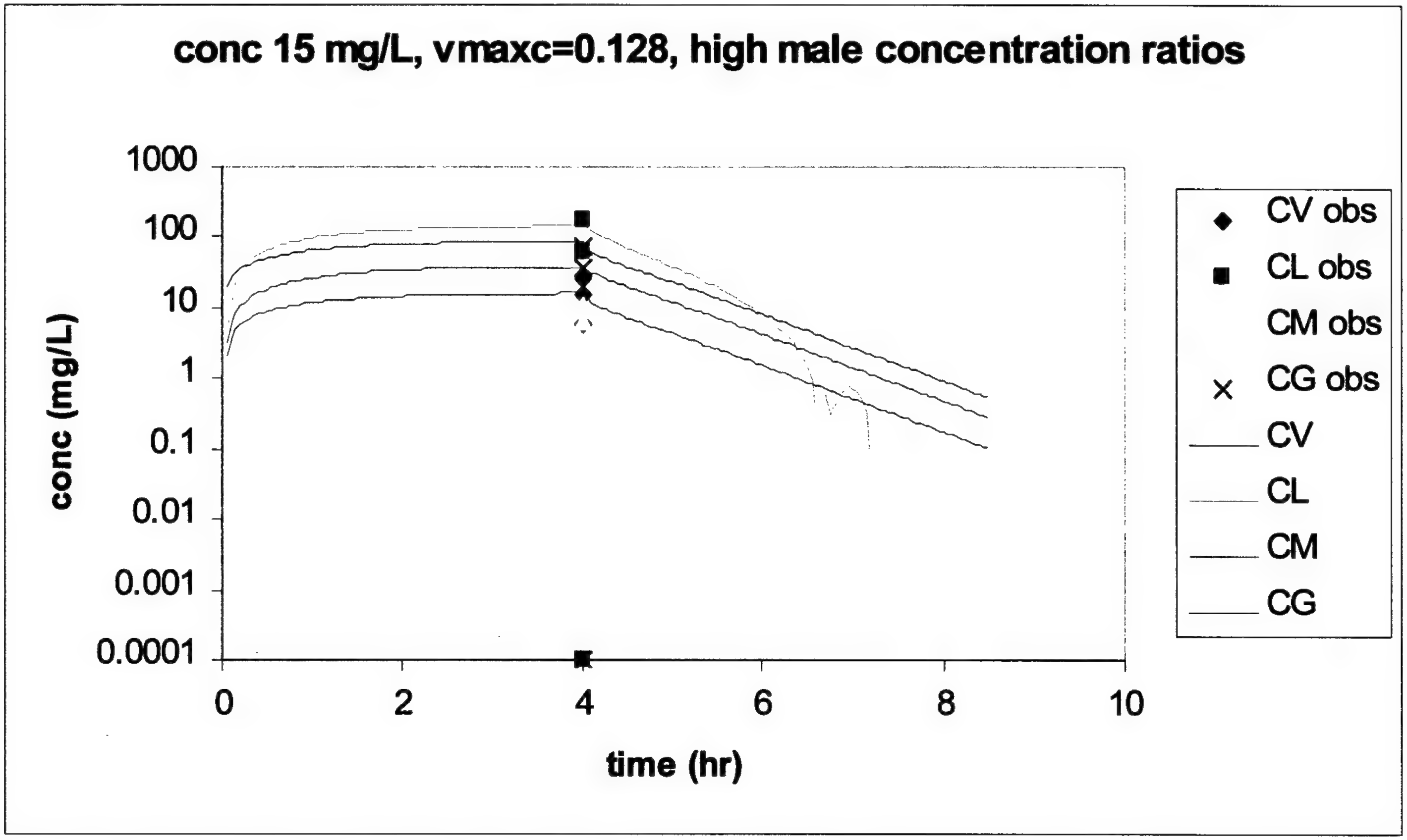
Appendix III. PBPK Plot Simulations



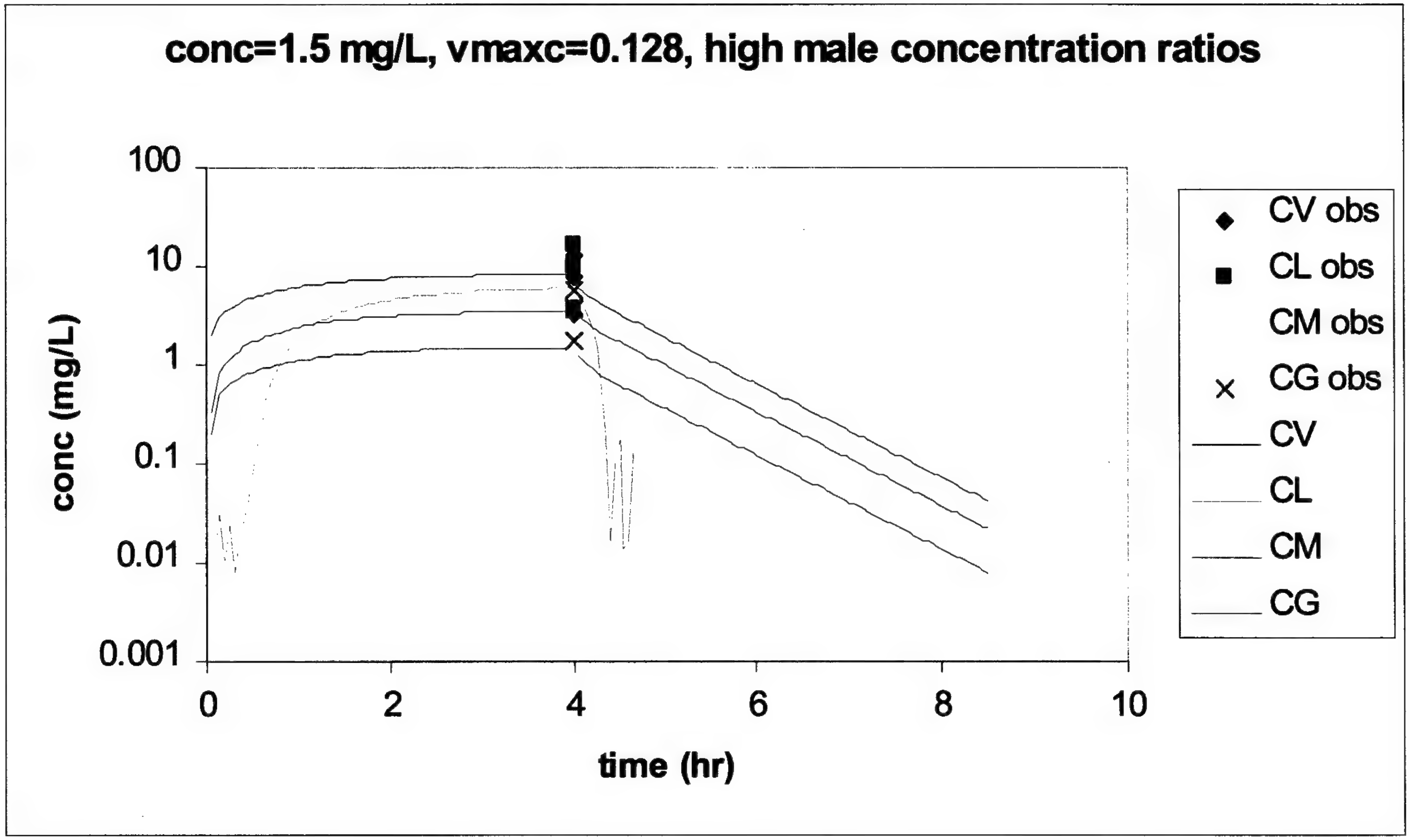
Plot III: High dosed male medaka, using high dose male concentration ratios as partition coefficients, and Vmaxc set to 0.0128 (acceptable, slight over prediction in CV and CM).



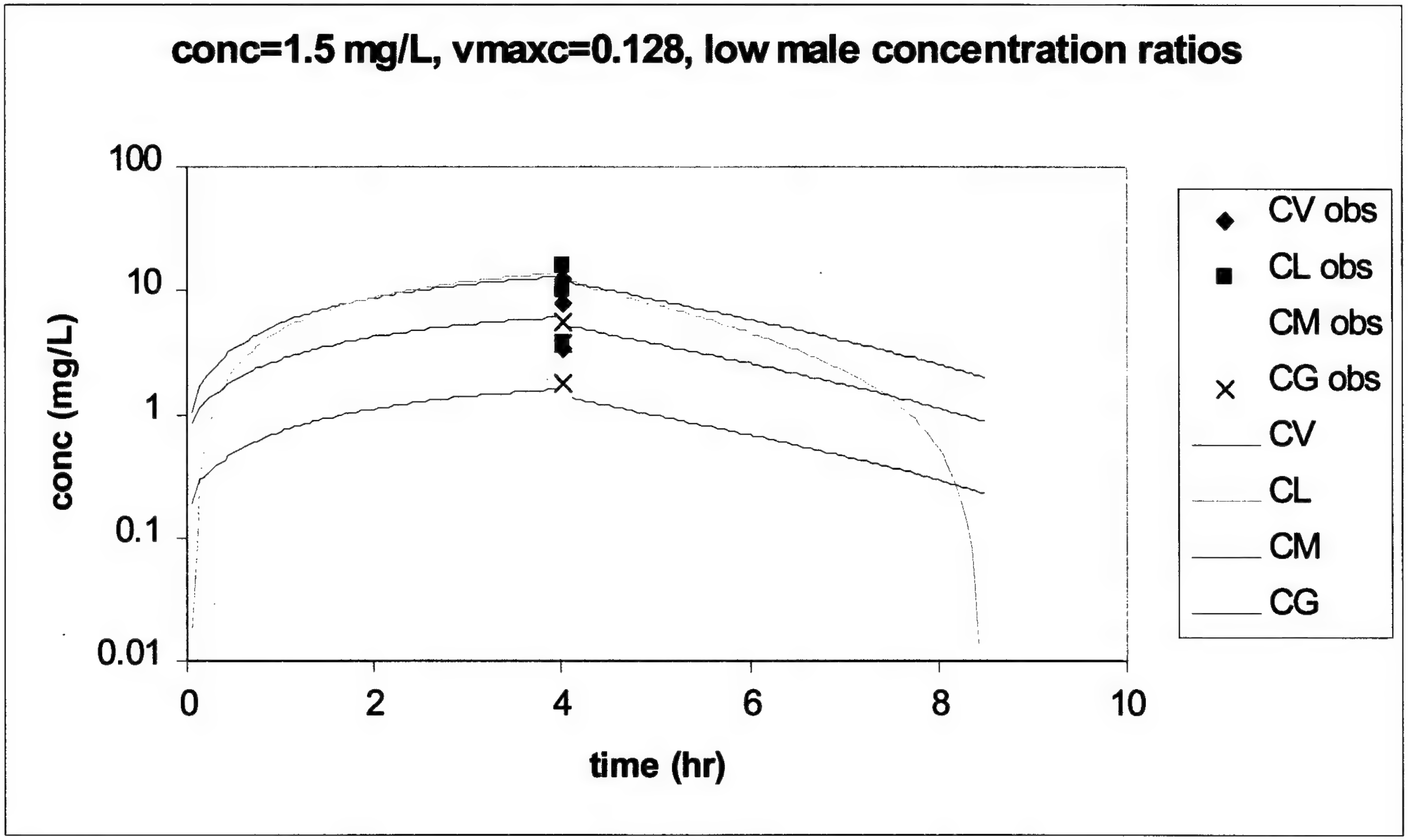
Plot IV: High dosed male medaka using high dose male concentration ratios as partition coefficients, and Vmaxc set to 0.0128. (same as Plot III but without the "other" compartment.



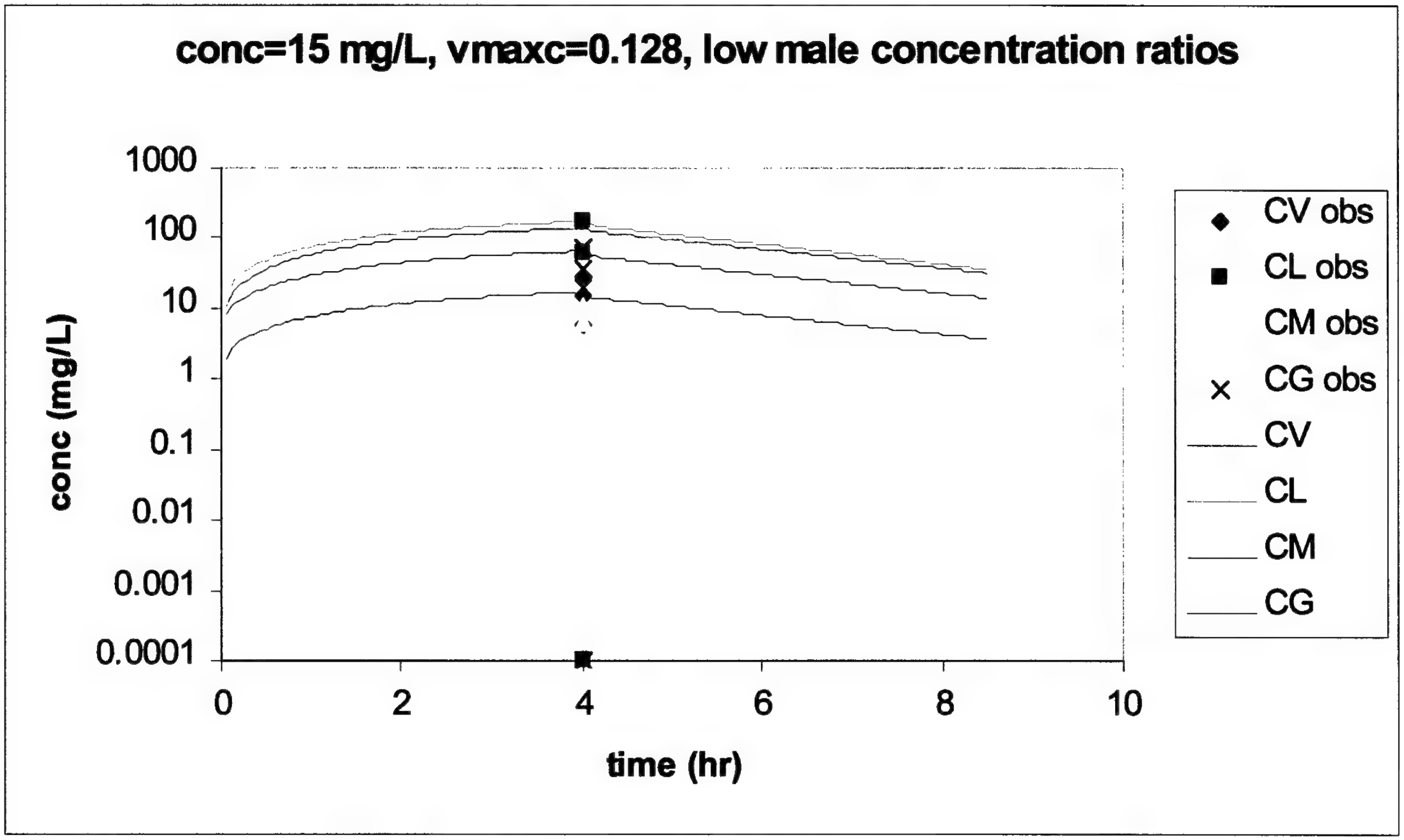
Plot V: High dosed male medaka using high dose male concentration ratios as partition coefficients, Vmaxc set at 0.128



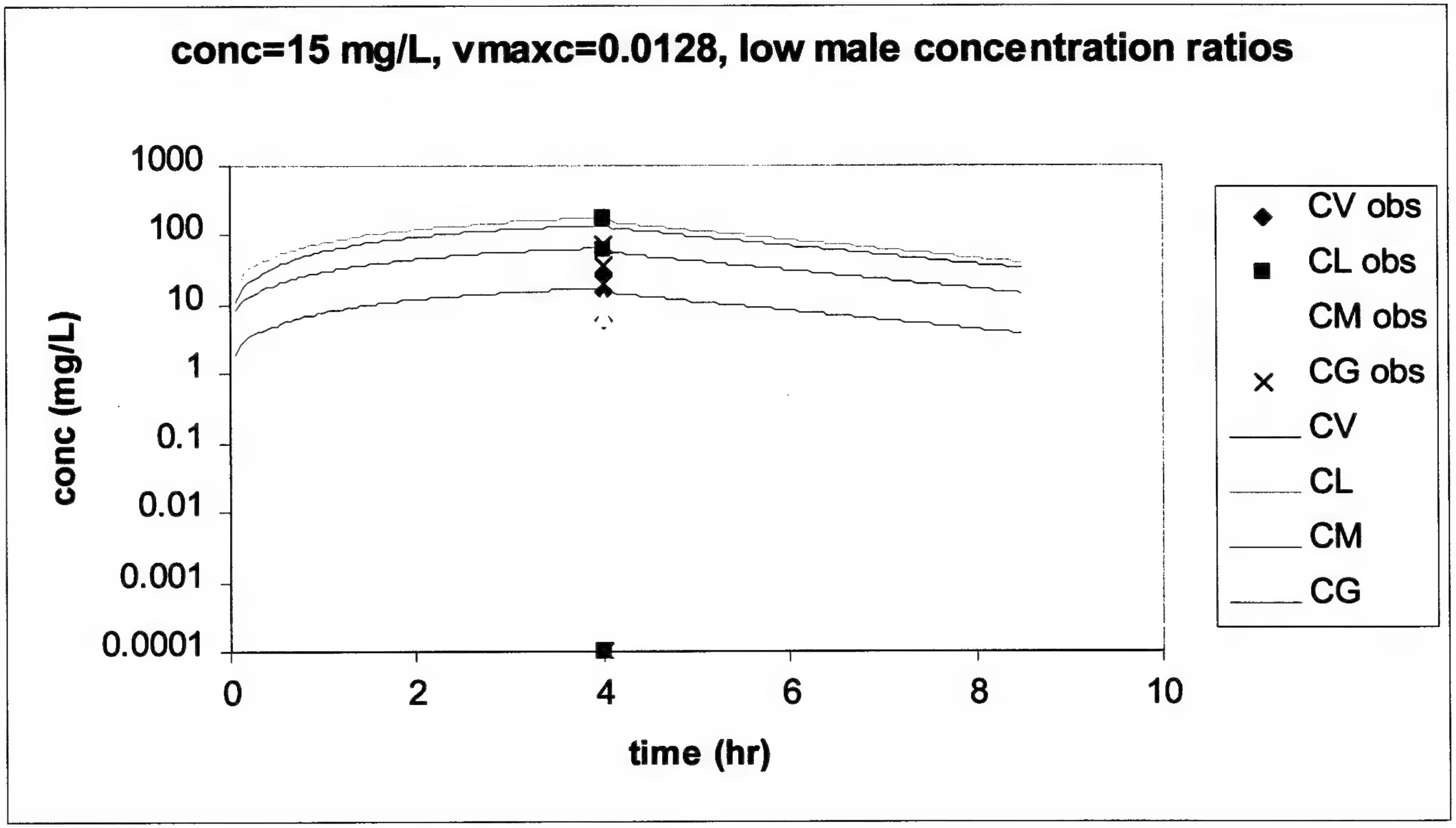
Plot VI: Low dosed male medaka using high dose male concentration ratios as partition coefficients, Vmaxc set at 0.128 (unacceptable, CL and CG far outside 1sd range).



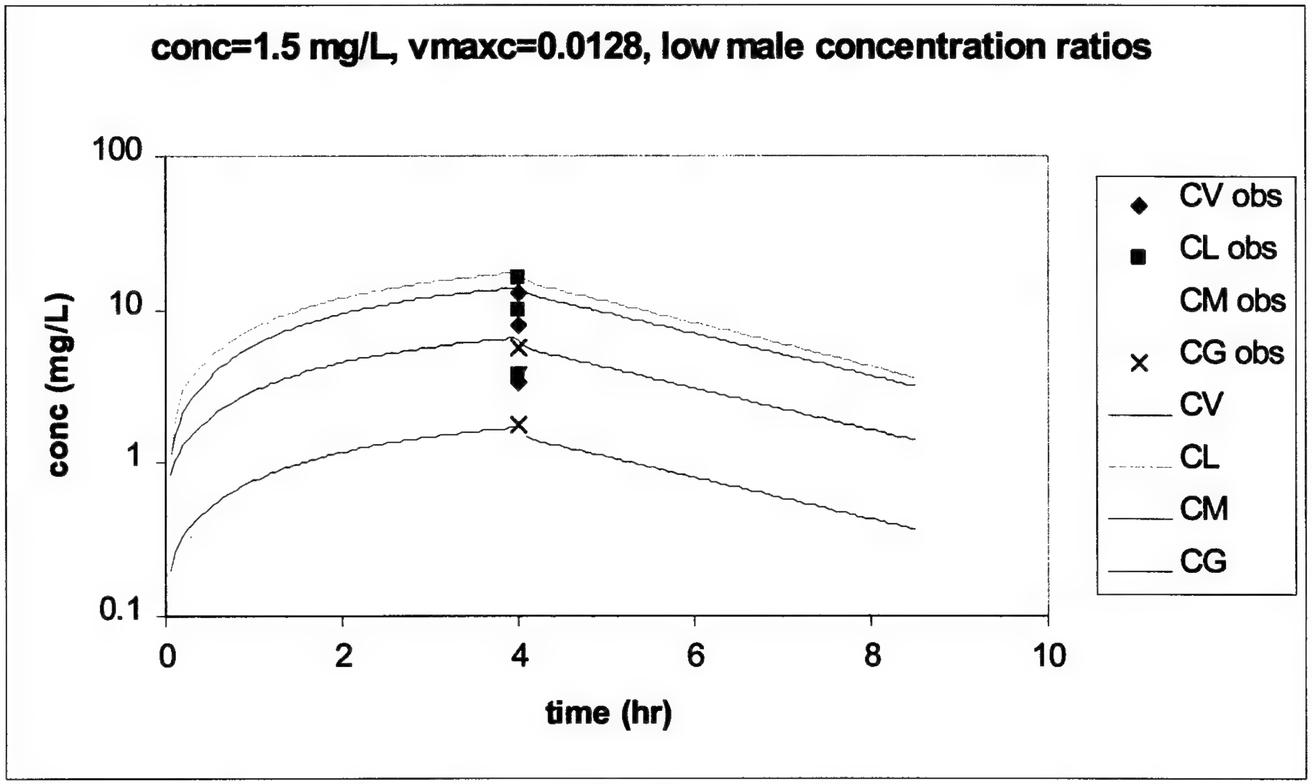
Plot VII: Simulation of low dosed male medaka, using low dose male concentration ratios as partitions, and Vmaxc set at 0.128 (an acceptable result).



Plot VIII: Simulation of high dosed male medaka, using low dose male concentration ratios as partitions, and Vmaxc set at 0.128. (an unacceptable result due to the fact that CV simulated concentrations were far outside the 1sd range).



Plot IX: Simulation of high dose male medaka, using low dosed male concentration ratios as partitions, and Vmaxc set at 0.0128 (unacceptable due to CV and CM both falling outside their 1sd ranges)



Plot X: Simulations of low dose male medaka, using low dose male concentration ratios as partitions, and Vmaxc set at 0.0128 (acceptable).

Appendix IV. Statistical values for histopathology endpoints of Test 108-002 (highlighted values are significant at $p = 0.05$)

Histology Endpoint	BDCM Treatment	No DEN female	No DEN male	No DEN Sexes Comb.	With DEN female	With DEN male	With DEN Sexes Comb.
Gallbladder Concretions	1.468 mg/L	2.103E-01	1.000E+00	4.967E-01	5.005E-01	1.000E+00	2.470E-01
	14.885 mg/L	7.284E-06	1.511E-03	1.894E-08	2.754E-03	3.099E-06	6.231E-09
Gallbladder, hyperplasia epithelium	1.468 mg/L	3.290E-01	6.125E-02	3.356E-02	3.118E-02	2.555E-02	3.655E-04
	14.885 mg/L	1.879E-03	2.227E-01	1.134E-03	6.645E-02	8.836E-05	9.423E-06
Liver, cholangiocarcinoma	1.468 mg/L	3.864E-02	2.901E-02	1.397E-03	1.144E-02	1.116E-02	1.336E-04
	14.885 mg/L	1.741E-01	9.745E-02	1.583E-02	4.969E-01	4.286E-01	1.085E-01
Liver, hepatocellular adenoma	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	4.615E-01	2.356E-01	1.000E+00
	14.885 mg/L	4.219E-01	1.000E+00	4.453E-01	3.673E-01	4.671E-03	3.417E-03
Liver, hepatocellular adenoma, multiple	1.468 mg/L				1.000E+00	-	-
	14.885 mg/L				1.000E+00	-	-
Liver, hepatocellular carcinoma	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	4.219E-01	1.000E+00	4.453E-01	1.000E+00	1.805E-01	1.085E-01
Liver, basophilic focus	1.468 mg/L				1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L				2.620E-02	3.024E-02	4.431E-04
Liver, Eosinophilic focus	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	6.783E-01
	14.885 mg/L	1.000E+00	4.687E-01	4.453E-01	2.702E-01	1.581E-01	2.206E-02
Liver, Concretions, bile ducts	1.468 mg/L	4.091E-04	1.511E-03	9.718E-07	6.289E-05	7.232E-05	4.554E-09
	14.885 mg/L	1.702E-04	9.116E-06	1.166E-09	4.784E-04	1.776E-03	1.738E-07
Liver, Dilatation bile ducts	1.468 mg/L	1.683E-03	3.160E-05	4.900E-08	1.648E-04	1.033E-02	4.918E-06
	14.885 mg/L	5.049E-05	4.360E-05	2.315E-09	6.788E-03	1.336E-01	1.753E-03
Liver, hyperplasia bile ducts	1.468 mg/L	4.143E-02	2.004E-03	7.250E-05	5.107E-03	3.135E-03	2.515E-05
	14.885 mg/L	1.529E-01	2.106E-02	2.689E-03	2.963E-03	3.798E-02	7.326E-05

Appendix IV. Statistical values for histopathology endpoints of Test 108-002 (highlighted values are significant at p = 0.05)

Histology Endpoint	BDCM Treatment	No DEN female	No DEN male	No DEN Sexes Comb.	With DEN female	With DEN male	With DEN Sexes Comb.
Bone, 1.468 mg/Ler jaw malformation	1.468 mg/L	4.559E-01	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	5.016E-04	9.750E-02	7.582E-05	2.453E-01	1.805E-01	2.362E-02
Bone, upper jaw, dysplastic cartilage	1.468 mg/L	1.404E-01	4.572E-01	8.807E-02	1.000E+00	8.234E-01	1.000E+00
	14.885 mg/L	1.635E-04	9.485E-04	2.438E-07	1.139E-06	2.233E-02	5.777E-06
Bone, vertebrae abnormal curvature	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	7.020E-02	4.687E-01	3.703E-02	4.969E-01	4.342E-01	1.110E-01
Bone, Vertebrae dysplasia, Caudal	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	1.090E-07	9.116E-06	1.109E-12	4.784E-04	1.144E-05	1.723E-09
Bone vertebrae dysplasia, Cranial	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	2.762E-02	5.195E-04	1.156E-05	2.453E-01	5.066E-03	1.075E-03
Bone, vertebrae dysplasia, Middle	1.468 mg/L	1.000E+00	4.977E-01	4.965E-01	1.000E+00	4.941E-01	1.000E+00
	14.885 mg/L	1.000E+00	4.313E-02	3.703E-02	1.203E-01	3.189E-02	2.385E-03
Gill, fusion, gill lamellae	1.468 mg/L	3.386E-02	3.889E-01	3.341E-02	5.883E-05	6.276E-07	9.233E-11
	14.885 mg/L	3.372E-03	8.258E-05	8.474E-07	2.983E-03	9.960E-03	4.765E-05
Gill hyperplasia, gill epithelium	1.468 mg/L	4.559E-01	2.465E-01	1.198E-01	4.932E-01	4.884E-01	2.447E-01
	14.885 mg/L	1.702E-04	1.322E-03	2.271E-07	4.784E-04	6.598E-04	6.829E-06
Gill, malformed arches	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	5.016E-04	7.920E-03	4.425E-06	2.820E-02	4.671E-03	8.411E-05
Gill, Malformed filaments	1.468 mg/L	2.041E-01	1.000E+00	6.197E-01	4.932E-01	4.944E-01	1.000E+00
	14.885 mg/L	4.526E-11	5.564E-07	3.976E-17	5.094E-10	7.693E-10	2.992E-19

Appendix IV. Statistical values for histopathology endpoints of Test 108-002 (highlighted values are significant at p = 0.05)

Histology Endpoint	BDCM Treatment	No DEN female	No DEN male	No DEN Sexes Comb.	With DEN female	With DEN male	With DEN Sexes Comb.
Thyroid, decreased follicles	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	4.219E-01	9.745E-02	3.703E-02	1.000E+00	1.090E-02	1.031E-02
Thyroid, increased basophilia	1.468 mg/L	6.534E-01	5.229E-06	1.727E-05	5.895E-01	1.608E-01	1.288E-01
	14.885 mg/L	5.045E-01	1.000E+00	6.282E-01	1.929E-01	9.955E-14	2.936E-13
Kidney, Mineralization	1.468 mg/L	4.559E-01	1.000E+00	1.000E+00	4.615E-01	6.118E-01	1.000E+00
	14.885 mg/L	3.948E-03	1.994E-01	3.856E-03	6.327E-02	3.798E-02	1.818E-03
Kidney, Tubular Casts	1.468 mg/L	1.000E+00	9.134E-03	2.626E-02	4.932E-01	3.607E-01	7.164E-01
	14.885 mg/L	4.512E-03	7.814E-01	2.164E-02	1.337E-03	2.123E-03	1.988E-05
Kidney, Tubular Degeneration	1.468 mg/L	1.000E+00	1.215E-01	1.198E-01	-	1.000E+00	4.928E-01
	14.885 mg/L	4.219E-01	4.313E-02	1.583E-02	2.453E-01	5.732E-01	1.049E-01
Kidney, Tubular dilatation	1.468 mg/L	1.000E+00	1.088E-01	2.924E-01	3.242E-01	4.845E-01	1.541E-01
	14.885 mg/L	2.995E-01	5.906E-01	8.356E-01	1.896E-01	2.502E-01	7.817E-02
Heart, Mineralization	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	4.219E-01	2.158E-01	8.571E-02	4.969E-01	7.459E-02	2.362E-02
Pseudobranch, Concretions	1.468 mg/L	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00	1.000E+00
	14.885 mg/L	7.020E-02	4.687E-01	3.703E-02	6.204E-01	1.805E-01	1.049E-01
Ovary, Early Vitellogenic Stage	1.468 mg/L	4.940E-01	-	-	6.521E-01	-	-
	14.885 mg/L	6.236E-10	-	-	7.815E-11	-	-
Ovary, Late Vitellogenic Stage	1.468 mg/L	1.000E+00			1.000E+00		
	14.885 mg/L	1.000E+00			4.969E-01		
Ovary, Previtellogenic Stage	1.468 mg/L	1.000E+00			3.242E-01		

Appendix IV. Statistical values for histopathology endpoints of Test 108-002 (highlighted values are significant at p = 0.05)

Histology Endpoint	BDCM	No DEN			With DEN		
	Treatment	female	male	Sexes Comb.	female	male	Sexes Comb.
	14.885 mg/L	1.792E-01			1.896E-01		
Ovary, Undeveloped	1.468 mg/L	1.000E+00			1.000E+00		
	14.885 mg/L	8.797E-08			1.001E-06		